THE ROLE OF FATIGUE, DEPRESSION AND OTHER CLINICAL FACTORS IN DETERMINING COGNITIVE STATUS IN PEDIATRIC MULTIPLE SCLEROSIS AND TRANVERSE MYELITIS

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DEDICATION

To my mother and father for giving me every opportunity; but especially to my mother for shepherding me through some of my darkest days. Love you up to the moon and back.

THE ROLE OF FATIGUE, DEPRESSION, AND OTHER CLINICAL FACTORS IN DETERMINING COGNITIVE STATUS IN PEDIATRIC MULTIPLE SCLEROSIS AND TRANSVERSE MYELITIS

by

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Abstract

Multiple sclerosis (MS) and transverse myelitis (TM) are immune-mediated demyelinating diseases of the central nervous system (CNS). MS is a chronic inflammatory disease that impacts both the brain and spinal cord; whereas, TM is a monophasic condition impacting only the spinal cord. Not surprisingly, cerebral involvement present in MS has precipitated research documenting deficits in cognition and problems related to fatigue and depression. Few studies have examined the prevalence of cognitive impairment or the role of fatigue and depression in cognitive functioning in pediatric patients with TM. Limited evidence suggests that both youth with MS and TM are at risk for adverse neuropsychological outcomes, less is known about underlying clinical factors that may influence cognitive functioning. Consequently, the objective of the present study was to explore the role of fatigue, depression, and disease-related clinical variables (physical functioning, age at onset, time since onset) in determining the cognitive status (i.e., impaired or not impaired) in youth with MS and TM. Sixty-seven pediatric MS and 53 pediatric idiopathic TM participants were administered a brief neuropsychological screening evaluation as part of routine clinical care. Analyses examining parent-proxy rating of fatigue and depression revealed no significant differences between MS and TM groups. Additionally, a logistic regression was conducted to evaluate the impact of a proposed linear combination of predictor variables in determining cognitive status (i.e., impaired or not impaired). Results revealed that none of the predictor variables were significant contributors to cognitive status. However, a stepwise logistic regression revealed that increased parent-proxy ratings of depression symptoms contributed to the likelihood that MS and TM participants were defined as cognitively impaired. Additionally, exploratory analyses revealed that youth with MS (42%) experience a significantly higher rate of cognitive impairment than youth with TM (21%).

Analyses found that both youth with MS and TM were rated as having a greater number of fatigue symptoms than would be expected in healthy controls, though they were not more likely to be rated as having depression symptoms. Findings of the present study suggest that youth with MS and youth with TM should undergo routine screening of cognitive functioning, as well as fatigue and depression symptoms. Such routine screenings would not only assist with identification of problems, but also facilitate the creation and implementation of interventions to address them. Research would likely benefit from additional studies examining the influence of fatigue and depression symptoms on cognitive functioning in MS and TM, albeit with larger sample sizes and additional metrics for assessing cognition, fatigue, and depression symptoms.

Keywords: Demyelinating; Pediatric; Neuropsychology; Multiple Sclerosis; Transverse Myelitis; Fatigue; Depression; Cognitive Impairment

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CHAPTER ONE
Introduction

Immune-mediated central nervous system (CNS) demyelinating diseases impact various areas of the brain, optic nerves, and/or spinal cord. This disruption of typical neurologic function can result in a number of diverse symptoms, including changes in cognitive, sensory and motor functioning. CNS demyelinating diseases include multiple sclerosis (MS) and transverse myelitis (TM), among others, including new conditions being described. Although the literature describing neuropsychological sequelae of CNS demyelinating diseases has primarily focused on adults with these conditions, evidence suggests that pediatric patients with demyelinating diseases also experience cognitive problems (Amato et al., 2008, 2010; Charvet et al., 2014; Harder, Holland, Frohman, Graves, & Greenberg, 2013; Holland, Graves, Greenberg, & Harder, 2014; MacAllister et al., 2013; Tan, Hague, Greenberg, & Harder, 2018). To date, the pediatric demyelinating diseases literature has primarily focused on describing the cognitive and psychosocial functioning of children with MS, while less is known about neuropsychological outcomes associated with TM (Tan et al., 2018).

MS is a chronic inflammatory condition impacting both the brain and spinal cord (Compston & Coles, 2008). By contrast, TM is a monophasic disease impacting the spinal cord only (Krishnan, Kaplin, & Deshpande, 2004). The cerebral involvement in MS has spurred research which has documented multiple areas of difficulty in pediatric patients with MS, including deficits in cognition and problems related to fatigue and depression (Holland et al., 2014; Julian & Harnett et al., 2009; MacAllister et al., 2005). In comparison, few studies have examined the presence of cognitive impairment, or the role of fatigue and depression in cognitive functioning in pediatric patients with TM (Tan et al., 2018). The limited available evidence suggests that children with TM are also at risk for adverse neuropsychological outcomes (Harder

et al., 2013). These findings are intriguing, given that the pathogenesis of TM does not have obvious cerebral involvement. Due to the similarities but also notable differences between MS and TM groups, as well as limited study of TM, comparing outcomes in these groups is valuable for promoting greater understanding of pediatric demyelinating diseases. Furthermore, although the pediatric MS literature has examined associations between disease-related variables (e.g., fatigue, depression) and cognitive functioning to some extent, the role of these factors in predicting cognitive functioning in pediatric MS or TM is currently unclear.

With regard to cognitive impairment, pediatric MS research has documented multiple domains of cognitive dysfunction, with approximately one-third of patients meeting criteria for cognitive impairment (Amato et al., 2008; Amato et al., 2014; Julian et al., 2013; Till et al., 2011). In comparison, only one study has examined the neuropsychological functioning of children with TM, which found wide-ranging cognitive deficits, despite group mean scores generally falling in the average range (Harder et al., 2013). High rates of parent-proxy reported fatigue were also found in this study, which may raise important questions regarding the possible role of fatigue in the cognitive functioning of children with TM. High rates of fatigue reported in children with TM are concerning due to fatigue's association with cognitive performance documented in the pediatric MS literature (Amato et al., 2008; Holland et al., 2014; MacAllister et al., 2005). Although research has identified a link between fatigue and cognitive function in children with MS (Charvet et al., 2016; Holland et al., 2014), the nature of the relationship between fatigue and cognitive impairment in either pediatric MS or TM has not yet been clarified.

Research regarding mood has found that children with MS are at-risk for various psychiatric problems (Tan et al., 2018), symptoms of which have been shown to correlate with

poorer performance in aspects of cognitive functioning in this population (Holland et al., 2014; Weisbrot et al., 2014). Despite these findings, our understanding of the relationship between cognitive impairment and mood-related symptoms in pediatric MS remains limited. Likewise, the existing literature is even more limited in terms of exploration of the relationship between these factors in pediatric TM. Although Harder et al. (2013) qualitatively assessed symptoms of depression in relation to cognitive functioning, there was no obvious association and to date, research directly examining the relationship between mood and cognitive functioning in pediatric TM has yet to be published.

Research on disease-specific clinical factors and cognitive functioning in pediatric MS has yielded inconsistent findings. While some pediatric MS studies have found associations between age at onset, time since disease onset, and/or disability status with cognitive impairment (Charvet et al., 2014; Houssieni et al., 2014; MacAllister et al., 2005; Till et al., 2013), other studies have found no correlation (Amato et al., 2008; Amato et al., 2014; Banwell & Anderson, 2005; Holland et al., 2014). In comparison, the role of clinical factors (i.e., age at onset, time since disease onset) as they relate to cognitive status have yet to be explored in pediatric TM.

Although emerging evidence suggests that youth with MS and TM are at risk for adverse neuropsychological outcomes, less is known about underlying clinical factors that may influence this outcome. Investigating these factors will not only promote greater understanding of pediatric demyelinating diseases by elucidating the prevalence of disease-related symptoms and examining their impact on cognitive functioning, but also has the potential to clarify target areas for intervention. Consequently, the proposed study seeks to explore the role of fatigue, depression, and disease-related clinical variables (physical functioning, age at onset, time since

disease onset) in determining the cognitive status (i.e., impaired or not impaired) in children with MS and TM.

CHAPTER TWO
Review of the Literature

Multiple Sclerosis

Prevalence and Demographic Factors

The prevalence of MS in the United States (US) was previously estimated to be approximately 0.15%, with around 400,000 adults currently living with the disease (MacAllister et al., 2013). The number of new MS diagnoses per year has been estimated to be 1 in 700, with a peak in age at onset around 30 years of age (Ascherio & Munger, 2008). A 2007 study estimated that approximately 1.25 million people were living the MS worldwide, and noted that the condition is considered to be the most common disabling neurological disease in young adults (Hirtz et al., 2007). A more recent study of the cumulative prevalence of MS in the United States from years 2008 to 2010 estimated a prevalence rate of approximately 100 to 200 per 100,000, with approximately 900,000 adults in the US currently living with the condition (Wallin et al., 2017). Results from this study indicate the highest reported prevalence of MS to date.

In contrast, MS emerging prior to 18 years of age (pediatric-onset MS; Krupp, Banwell, & Tenembaum, 2007) is generally considered a rare neurological condition. Pediatric onset is estimated to occur in 2 to 5% of all patients diagnosed with MS, with onset typically occurring during teenage years (Boiko, Vorobeychik, Paty, Devonshire, & Sadovnick, 2002; Chitnis, Glanz, Jaffin, & Healy, 2009; Duquette et al., 1987; Ghezzi et al., 1997; Simone, Carrara, Tortorella, Ceccarelli, & Livrea, 2000; Yamamoto, Ginsberg, Rensel, & Moodley, 2018). Research has noted that pediatric MS is diagnosed at a lower rate in children under pubertal age: specifically, between 0.2% and 0.7% of all cases are diagnosed under age 10 (Alroughani & Boyko, 2018; Boiko et al., 2002). Given the rarity of pediatric MS, less is known about clinical

outcomes and the degree to which disease-related factors, such as age at onset or time since disease onset, relate to outcomes in youth with this condition.

Consistent with sex ratios in adults with MS, girls are disproportionately represented in pediatric MS cases; however, it is important to note that female-to-male ratios vary with age (MacAllister et al., 2013). For example, in children under the age of 6, the female-to-male ratio is about 0.8:1. In contrast, in children between the ages of 6 and 10, the ratio is 1.6:1 while the ratio for children with disease onset after age 10 is approximately 2:1 (Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007; Banwell, Krupp, et al., 2007; Renoux et al., 2007).

Interestingly, research has indicated that pediatric MS differs from adult MS in racial and ethnic makeup. In adults, MS predominately impacts people who are Caucasian and are of Northern European Heritage (Harder, Bobholz, & MacAllister, 2018; Koch-Henriksen & Sørensen, 2010). In contrast, studies of demographic factors in pediatric-onset MS have revealed that youth with MS are more diverse than their adult counterparts (Kennedy et al., 2006). Specifically, research has found that Black or African American children are more vulnerable to the disease than Caucasian children (Chitnis et al., 2009).

Clinical Presentation and Etiology

Clinical presentation. MS is a chronic inflammatory immune-mediated disorder of the CNS, which results in demyelination of axons in the brain, optic nerves, and spinal cord and secondary axonal damage (Krupp, Banwell, & Tenembaum, 2007). Damage to the CNS produces a variety of neurologic symptoms that tend to vary in type and severity among patients diagnosed with the disease (Krupp et al., 2007). This variability contributes to MS being considered a highly heterogenous disorder (Disanto et al., 2011).

In the majority of adult patients (80%), clinical features often involve motor, sensory, visual, and/or autonomic systems, resulting from a demyelinating event (Compston & Coles, 2008). Since demyelinating events can occur in any area of the brain, optic nerve, and/or spinal cord, disease presentation may include a diverse array of neurologic symptoms. Although there are no clinical symptoms that are unique to MS, some are highly characteristic of the condition, including: visual disturbance (e.g., diplopia) or vision loss, motor (e.g., weakness, gait and balance problems), sensory symptoms (e.g., numbness and tingling), and autonomic dysfunction (e.g., bowel, bladder, or brainstem dysfunction). Importantly, clinical presentations can range from monofocal to multifocal symptom presentations (Richard, Sampson, Beard, & Tappenden, 2002).

Similar to the adult MS population, youth with MS present with multifarious clinical features. More than 50% of children have multifocal presentations (Banwell et al., 2007), resulting in multiple symptoms, such as vision loss, motor (e.g., weakness, spasticity, gait problems, and balance difficulties), and/or sensory problems (e.g., numbness and tingling), as well as bowel, bladder, and/or brainstem dysfunction. Seizures have been found to occur in an estimated 5% of children with MS but appear to most frequently emerge in younger children (Banwell et al., 2007). Importantly, clinical presentations of pediatric MS may be related to differences in the pathogenesis of the disease in children and adolescents (MacAllister et al., 2013; National Multiple Sclerosis Society [NMSS], 2018).

Neurologists acknowledge four major categories of MS based on the time course of the disease (Lublin et al., 2014): Relapsing–remitting MS is the most common form of the disease, affecting an estimated 85% of adult patients diagnosed with the condition. This disease course is characterized by flare-ups or exacerbation of symptoms, referred to as relapses, following

periods of remission, when symptoms improve or remit. The secondary progressive course of MS—which may develop in patients who were initially diagnosed with the relapsing–remitting form of the disease—is characterized by continual worsening of disease symptoms without periods of plateau or remission. Primary progressive MS impacts around 10% of all MS adult patients. Symptoms of the primary progressive course continue to worsen gradually following the onset of the disease. Although patients with primary progressive MS do not experience relapses or remissions, they may experience occasional plateaus. This form of MS tends to be more resistant to treatment. Progressive-relapsing MS is a rare form of the disease, impacting less than 5% of patients diagnosed with the condition. As the name implies, progressive-relapsing MS is distinguished by an immediately progressive course with intermittent flare-ups of worsening symptoms throughout, without periods of remission.

Pediatric patients with MS are diagnosed with a relapse-remitting course 98% of the time, compared to 85% of adult patients (Renoux et al., 2007). Furthermore, children with MS are less likely to develop primary or secondary progressive MS under the age of 18 (Renoux et al., 2007). Studies have noted that relapses are more frequent in pediatric patients with MS than adults (Gorman, Healy, Polgar-Turcsanyi, & Chitnis, 2009). It has been posited that a large number of youths with MS will be subsequently diagnosed with the progressive form of the disease by age 30 (Banwell et al., 2007). It has also been suggested that a small portion of youth diagnosed with pediatric MS will become severely disabled later in life (Banwell et al., 2007).

Etiology. Although the cause of MS remains unclear, the literature suggests that disease onset is thought to be the result of an interaction between a genetically predisposed individual's exposure to a combination of environmental factors (Ascherio & Munger, 2008). Importantly, research investigating this interaction between environmental factors and susceptible individuals

has primarily focused on adults with MS (Ascherio & Munger, 2008). The study of etiological factors in pediatric MS has focused on the role of common viruses experienced in this population due to the temporal proximity between exposure to such viruses and disease onset (MacAllister et al., 2013). Additionally, MS has been identified as a partially heritable autoimmune disease (Parnell & Booth, 2017). For identical twins, the risk of developing MS increases to approximately 1 in 4 when one twin is affected. The heritability of MS is explained almost entirely by genes affecting the immune response (Parnell & Booth, 2017).

The role of Vitamin D has been thoroughly described in the adult MS literature (Ascherio & Munger, 2008). Specifically, multiple studies have found an inverse association between sun exposure, exposure to ultraviolet light, or serum vitamin D levels, and the risk of developing MS or prevalence of MS (Islam, Gauderman, Cozen, & Mack, 2007; Munger et al., 2004; Salzer et al., 2012; van der Mei et al., 2003). Furthermore, a longitudinal study of 469 adults with MS found that higher vitamin D levels were inversely associated with the risk of developing new brain lesions on MRI (Mowry et al., 2012). Emerging evidence suggests that vitamin D also plays an important role in pediatric MS (Mowry et al., 2010; Mowry, 2011). For instance, lower levels of serum Vitamin D were independently associated with a higher relapse rate in already-diagnosed pediatric MS patients (Mowry et al., 2010; Mowry, 2011).

Much of the research investigating vitamin D as it relates to risk of developing MS was due to early studies that documented a latitudinal gradient for MS. Specifically, this body of work identified a trend toward an increasing incidence of MS with greater distance from the equator (e.g., Kurtzke, 1980). Consequently, MS has historically been viewed as more common in people from northern states in the US (Simpson, Blizzard, Otahal, van der Mei, & Taylor, 2011). Notably, research has documented that living in areas with high ambient ultraviolet light

during childhood and years preceding disease onset was associated with lower risk of developing MS (Tremlett, Zhu, Ascherio, & Munger, 2018). However, it is important to note that the impact of the latitudinal gradient has decreased over time with an increasing number of cases occurring further south (Alonso & Herman, 2008).

Regarding environmental risk factors, onset of pediatric MS has been associated with increased seropositivity to the Epstein Barr virus (EBV) when compared to age matched healthy controls (Alotaibi, Kennedy, Tellier, Stephens, & Banwell, 2004; Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007; Lünemann et al., 2008; Pohl et al., 2006). Additionally, exposure to cigarette smoke has been associated with increased risk of MS in children (Mikaeloff, Caridade, Tardieu, Suissa, & KIDSEP Study Group, 2007), consistent with findings in adults (Ascherio & Munger, 2008). Specifically, the relative risk for a first demyelinating event in children who were exposed to smoking was found to be more than twice the rate of the control group. Furthermore, longer duration of exposure to smoking was found to potentially place children at increased risk for a demyelinating event (Mikaeloff et al., 2007).

Within the past few years, studies have consistently found the presence of high-titer serum IgG antibodies to conformational epitopes of the myelin oligodendrocyte glycoprotein (MOG) in pediatric patients with demyelinating diseases (Reindl & Rostasy, 2015). As suggested by its name, MOG is a glycoprotein found in the outer membrane of the myelin sheath, though it exists solely in the central nervous system (Narayan et al., 2018). Recent research has suggested that documentation of anti-MOG antibodies can help distinguish demyelinating events that may mimic MS, which may assist with diagnosis, prognosis, and treatment of individuals with monophasic and recurrent demyelinating diseases (Reindl & Rostasy, 2015). It is possible that previous pediatric MS research inadvertently included subjects with this unique and specific

condition. While research on neuropsychological outcomes in individuals who are MOG-positive is certainly needed, a current challenge is the retrospective examination of previously-collected patient data which did not include identification of MOG antibodies. Therefore, while future research should seek to investigate the neuropsychological profiles of children who are MOG-positive, current studies may be limited due to sample size constraints.

Pathogenesis, Diagnosis, and Treatment

MS is a heterogeneous disorder with various potential pathologic features (Weiner, 2004). The current theory of MS pathogenesis is that the immune system incorrectly identifies the myelin of the CNS as a foreign entity and responds by sending disease-fighting cells to 'attack' and damage the myelin in the CNS. These autoimmune attacks result in inflammation, demyelination, and axonal degeneration in the CNS (Compston & Coles, 2008; Lassmann, Brück, & Lucchinetti, 2007). Immunopathologic features (i.e., immune responses associated with a disease) of MS include: inflammation occurring in conjunction with disruption to blood-brain-barrier function, which often precedes demyelinating lesions (i.e., plaques or scars) in patients with MS (Dargahi et al., 2017); the presence of two types of inflammatory white blood cells (T-cells and B-cells) and macrophages, viewed on histopathologic examination of MS lesions (Lucchinetti, Brück, Parisi, Scheithauer, Rodriguez, & Lassmann, 2000); and the presence of unique IgG oligoclonal bands in the cerebral spinal fluid (CSF).

Currently, there is no single diagnostic test for MS (Goldenberg, 2012). The primary requirement for a diagnosis of MS is damage to CNS that is disseminated in both space (i.e., occurring in different parts of the CNS) and time (i.e., two or more events occurring at different times throughout the disease course), with appropriate clinical features (i.e., chronic inflammation of the CNS) while ruling out potential mimics. These main criteria allow clinicians

to distinguish MS from other neurological diseases and conditions (Compston & Coles, 2008; Goldenberg, 2012; Lublin et al., 2014; Thompson et al., 2018). Of note, clinically-isolated syndrome (CIS) is a diagnostic category of demyelinating disease characterized by inflammatory demyelination that appears consistent with MS, but does not currently meet criteria (i.e., dissemination in time) for the condition (Lublin et al., 2014).

A neurological examination may assist in revealing signs consistent with past or current demyelinating events, including optic neuritis (e.g., visual deficits, or eye color desaturation), eye movement abnormalities (e.g., internuclear ophthalmoplegia), upper motor neuron signs (e.g., spasticity, hyperreflexia, Babinski sign), ataxia, gait disturbance, sensory deficits or loss, and paresthesias in the limbs. Revisions to the 2010 McDonald Criteria were made to assist with diagnosis and differentiation of MS from other demyelinating diseases and to aid in early identification and facilitating timely discussions of treatment and disease management (Polman et al., 2005; Thompson et al., 2018). While the advent of magnetic resonance imagining (MRI) and identification of biomarkers (e.g., the presence of unmatched oligoclonal bands in the CSF) has allowed clinicians to gather objective clinical evidence that is consistent with a diagnosis of MS, it should be noted that imaging findings are not required to diagnosis MS (Arrambide et al., 2018; Thompson et al., 2018).

MS is typically treated using a combination of pharmacological agents, known as disease-modifying therapies (DMTs), as well as adjunctive medications and supportive therapies (Pardo & Jones, 2017). To treat inflammation that occurs during an acute MS relapse, patients receive corticosteroids, specifically intravenous methylprednisolone (MacAllister et al., 2013). Alternatively, high-dose oral corticosteroids may be offered (MacAllister et al., 2013). It is important to note that treatment with corticosteroids is often associated with adverse side effects

(e.g., insomnia, psychosis, hyperglycemia, and hypertension), necessitating careful monitoring throughout treatment (MacAllister et al., 2013). If steroids prove to be ineffective during acute relapses, plasmapheresis is a potential alternative. Plasmapharesis has been found to be efficacious in youth and adults with MS (Duzova & Bakkaloglu, 2008).

DMTs are pharmacologic agents that target the inflammatory response in MS. These medications assist in reducing the chance of relapse in patients (i.e., decreasing the chance for new lesion formation; Vargas & Tyor, 2017). These agents can be administered orally, intravenously, as well as via intramuscular injection or subcutaneously. While several studies have found that DMTs used successfully in the treatment of adults are also well-tolerated and efficacious in reducing relapse rates in children and adolescents with MS (Ghezzi et al., 2007; Ghezzi & Immunomodulatory Treatment of Early Onset MS [ITEMS] Group, 2005; Pohl et al., 2005; Tenembaum & Segura, 2006; Waubant et al., 2001), there is currently only one medication, fingolimod, that is approved by the US Food and Drug Administration for use in pediatric MS (FDA; Chitnis et al., 2018).

Although research has primarily focused on treatment related to reducing relapse rates, additional medications are frequently used to treat symptoms such as those that relate to fatigue, depression, and cognitive symptoms. For example, to treat fatigue in both adults and children with MS, amantadine, modafinil, and methylphenidate have been used clinically (Pohl et al., 2007). Additionally, some stimulants used to treat fatigue (i.e., methylphenidate and modafinil) have been found to be effective in treating cognitive problems (attention, processing speed) in adults and children with MS (Harel, Appleboim, Lavie, & Achiron, 2009; Wilken et al. 2008). Depression symptoms in adults with MS are frequently treated using a selective serotonin

reuptake inhibitor (SSRI; Nathoo & Mackie, 2017), and are frequently used to treat children with mood dysfunction (MacAllister et al., 2013).

Neurocognitive Outcomes

Cognitive impairment in adults with MS has been well documented (Benedict, Weinstock-Guttman, & Fishman, 2004) and is estimated to occur in 40 to 60% of adults diagnosed with MS (Rao, Leo, Bernardin, & Unverzagt, 1991). Furthermore, cognitive impairment in adults with MS has been found to be associated with poorer occupational and social functioning (Amato, Zipoli, & Portaccio, 2006; Benedict et al., 2004; Gilchrist & Creed, 1994; Rao et al., 1991). Comparatively, research pertaining to cognitive outcomes in pediatric MS is limited (Tan et al., 2018), although the existing literature has identified the presence of neurocognitive impairment in approximately one-third of patients with pediatric MS (Amato et al., 2008; Julian et al., 2013; MacAllister et al., 2005). Regarding specific areas of impairment in pediatric MS, research has documented deficits in intellectual functioning, attention and executive functioning, visuomotor and visuospatial functioning, language, and memory (Blaschek et al., 2012; MacAllister et al., 2013; Suppiej & Cainelli, 2014). Despite these findings, the heterogeneity and complexity of neurocognitive outcomes (Nunan-Saah, Paulraj, Waubant, Krupp, & Gomez, 2015) and the pathogenesis of the disease makes it difficult to establish a clear neuropsychological profile in pediatric MS (Tan et al., 2018).

Differing empirical approaches to defining cognitive impairment also contribute to the lack of clarity regarding neuropsychological functioning in pediatric MS. There is no current consensus regarding what metric should be used to define cognitive impairment (Tan et al., 2018). For example, while some studies have used a composite or mean score of all tests administered to determine cognitive impairment (e.g., MacAllister et al., 2005), others have

defined cognitive impairment as a specific number of tests or domains failed (e.g., Julien et al., 2013). However, either of these methods of determining cognitive impairment present multiple problems. For example, poorer performance on a given test or in a given domain could result in a composite score suggestive of impairment even if most other areas are intact. Similarly, creating a cutoff for number of tests below a certain variably-defined threshold could negate important cognitive findings (Tan et al., 2018).

Moreover, in neuropsychological evaluations, a number of measures are typically administered to comprehensively assess the overall cognitive functioning of patients. This requires sampling patient performance in multiple cognitive domains, necessitating the administration of multiple measures. Consequently, assessing patients' functioning involves analyzing whether their performance differs from the performance of healthy controls on one or more of such measures. However, consideration of performance on individual measures separately entails an increased risk of a false positive (Type 1) error. Based upon this need to analyze multiple measures at the same time, the use of a multivariate analysis holds promise for improving methodology to define cognitive status in clinical research (Huizenga, Smeding, Grasman, & Schmand, 2007).

To evaluate the performance of a multivariate method, Huizenga et al. (2007) compared a Bonferroni corrected univariate approach against a Hotelling's T-squared (T^2) distribution multivariate model to infer cognitive impairment in both a clinical sample of patients with Parkinson's disease, and a sample of healthy controls. Both univariate and multivariate approaches were used to examine the neuropsychological functioning of participants in both samples. Simulations were performed to review the sensitivity and specificity of the model, as well as to examine the power of both models in detecting deviations from the norm. Results

indicated exceptional sensitivity and specificity of the T^2 distribution multivariate model for the inference of cognitive status in patients with Parkinson's disease and healthy controls, identifying a subset of patients with Parkinson's as cognitively impaired, while no healthy controls were identified as cognitively impaired. Results indicated that the multivariate approach is preferred in cases when multiple tests are administered, unless sample size is similar to the number of tests administered (Huizenga et al., 2007). To date, Huizenga et al.'s (2007) model is the only published multivariate approach to infer impairment from a battery of cognitive test based on the T^2 test.

Intellectual functioning. When compared to healthy, age-matched controls, several studies have found that pediatric patients with MS exhibited a lower group mean intelligence quotient (IQ) or higher rates of IQ deficits (Amato et al., 2008; Portaccio et al., 2009). It is important to note that these findings should be interpreted with caution, as overall mean IQ scores were still found to fall within normal limits in these studies, without conducting premorbid assessments of functioning (Tan et al., 2018). A recent study has also suggested that children with a higher cognitive reserve (interpreted as a higher full-scale IQ) may be protected against cognitive impairment and progression of neuropsychological deficits (Pasto et al., 2016). However, additional research is needed to clarify the impact of cognitive reserve in mitigating cognitive impairment in children with MS.

Language. Language appears to be a particularly vulnerable domain of functioning in pediatric MS (Suppiej & Cainelli, 2014). This may be secondary to interruption of the normal early brain development which continually cultivates linguistic skills throughout childhood. Regarding specific areas of language difficulty, children with MS have demonstrated difficulty with complex language functions, such as receptive language and sentence comprehension, as

well as verbal fluency skills (Amato et al., 2010; MacAllister et al., 2005). Additionally, deficits in expressive language and naming skills have also been identified (Pasto et al., 2016; Till et al., 2011). Problems with linguistic abilities have been found to be associated with overall cognitive impairment (Portaccio et al., 2009; Till et al., 2011).

Attention and information processing. Several studies have found that youth with MS have difficulty with aspects of complex attention, including shifting attention (Amato et al., 2008, 2010; Charvet, O'Donnell, et al., 2014; Julian et al., 2013). Deficits in slowed processing of both visuomotor and purely visual information are also frequently observed in the pediatric MS population (Julian et al., 2013; Smerbeck et al., 2011; Till et al., 2011). Studies that have identified deficits in attentional and information processing speed abilities also noted that such deficits are present early on in the disease course. These results are similar to findings in the adult MS population, which have found selective attention and impaired processing speed to be among the most prominent deficits in patients with MS (Prakash, Snook, Lewis, Motl, & Kramer, 2008).

Visuospatial and visuomotor skills. Deficits in visuospatial and visuomotor skills in pediatric MS have been identified, with visuomotor integration being most impacted (Charvet, O'Donnell, et al., 2014; Julian et al., 2013; MacAllister et al., 2005; Till et al., 2013). Importantly, findings regarding visuospatial and visuomotor deficits in the pediatric MS population should be interpreted with caution, as visual disturbances (Banwell, Krupp, et al., 2007) and deficits in fine motor speed and coordination are frequently reported in this population (Julian et al., 2013), which can contribute to visuospatial and visuomotor deficits. Deficits in visuospatial and spatial perception skills have also been observed in adults with MS (Rao, Leo, Ellington, et al., 1991; Vleugels et al., 2000).

Memory. Research has documented deficits in immediate and delayed recall for both verbal and visual memory in patients with pediatric MS (Amato et al., 2008; Fuentes et al., 2012). Particularly, evidence has identified difficulties with total learning, immediate, and delayed recall of verbal information in children with MS (Amato et al., 2010; MacAllister et al., 2005). These findings are consistent with adult MS research, which has shown verbal and nonverbal memory impairments occur in 40–60% of adults diagnosed with MS (Rao, Leo, Bernardin, & Unverzagt, 1991). Research has also implicated visual memory as an area of deficit in children with MS (Smerbeck et al., 2011), although findings relative to this domain are inconsistent (MacAllister et al., 2005).

Executive function. Executive functions are a series of interconnected, top-down mental processes that underlie certain behaviors, such as concentrating, attending, planning, initiating, and inhibiting behaviors (Diamond, 2013; (Shonkoff, Duncan, Fisher, Magnuson, & Raver, 2011). While impairments in aspects of executive functions (planning, cognitive flexibility) are well documented in adults with MS (Arnett et al., 1997; Penman, 1991), results regarding executive functioning in pediatric MS are less consistent. For example, some studies have indicated that children with MS experience deficits in working memory functions; however, these findings may be influenced by attentional abilities (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005). Other studies have described impairments in cognitive flexibility, planning, and initiation in samples of pediatric patients with MS (Amato et al., 2008; MacAllister, Christodoulou, Milazzo, & Krupp, 2007; Till, Ho, et al., 2012), while other studies found that patients performed within the normal range on measures of these skill areas (Banwell & Anderson, 2005; Deery, Anderson, Jacobs, Neale, & Kornberg, 2010). Interestingly, Holland et al. (2014) found heterogeneous results related to executive dysfunction in a sample of children

with MS. Of note, participants from this study are included in the current project. Specifically, the authors found that patients demonstrated lower performance on a measure of cognitive flexibility, but group means on measures of working memory and initiation were within normal limits. Such variable findings necessitate additional research into the executive functioning abilities of youth with MS.

Psychosocial and Clinical Outcomes

Fatigue. Fatigue has been described as an overwhelming feeling of tiredness and exhaustion, which is commonly experienced in healthy adults (Meng, Hale, & Friedberg, 2010), and often experienced in individuals with chronic medical conditions (Rosenthal, Majeroni, Pretorius, & Malik, 2008). Fatigue is the most commonly-reported symptom in adults with MS (Freal, Kraft, & Coryell, 1984; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Minden et al., 2006). Fatigue being the most prevalent symptom in adults with MS is concerning, as fatigue has also been found to be the most disabling symptom, resulting in occupational and social impairment, as well as interfering with physical functioning (Edgley, Sullivan, & Dehoux, 1991; Smith & Arnett, 2005).

In children and adolescents with MS, fatigue has also been found to be a prevalent symptom (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005, 2009). Specifically, pediatric MS research has found fatigue rates of up to 73% (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005). Because fatigue is not readily apparent in children, it has been considered a “hidden disability” (MacAllister et al., 2013, p. 11). As a result, symptoms of fatigue may be misinterpreted by peers, teachers, and others as activity avoidance (MacAllister et al., 2009). Research has also documented that high rates of fatigue are associated with deficits in various aspects of cognitive performance (Amato et al., 2008; Holland et al., 2014; MacAllister

et al., 2005). Consequently, additional research focused on clarifying the impact of fatigue on cognitive functioning is critical for understanding cognitive functioning in pediatric patients with MS.

Mood. An important factor to consider when investigating the neuropsychological functioning of adults and children with MS is psychological functioning. The prevalence of mood problems has been thoroughly researched in adults with MS (Ghaffar & Feinstein, 2007; MacAllister et al., 2013). In adult MS patients, high rates of depression (up to 70%) are observed (Baumstarck-Barrau et al., 2011; Nagaraj, Taly, Gupta, Prasad, & Christopher, 2013), which has also been found to be related to quality of life (Baumstarck-Barrau et al., 2011).

By comparison, research examining the psychological functioning of pediatric MS patients is relatively inchoate. Studies examining psychological functioning of pediatric MS have suggested that between one-third and 50% of children diagnosed with MS meet criteria for primarily internalizing psychiatric diagnoses (Amato et al., 2008; Goretti et al., 2010, 2012; MacAllister et al., 2005; Weisbrot et al., 2010). Consequently, researchers have concluded that children with MS are at-risk for psychological problems, requiring consistent monitoring and intervention (Goretti et al., 2010; MacAllister et al., 2005, 2013; Weisbrot et al., 2010).

Similar to findings in adults (Benedict et al., 2004), studies of pediatric MS have also indicated a relationship between cognitive dysfunction and psychosocial problems. Specifically, Charvet, Cersosimo, Schwarz, Belman, & Krupp (2016) found that cognitive functioning could predict the presence of clinical problems (e.g., problems with attention, somatization, and anxiety) in children with MS. Research has also found that emotional dysfunction (depression, anxiety) correlated with poorer performance on measures of executive functioning (Holland et al., 2014; Julian & Arnett, 2009). Furthermore, children with MS diagnosed with a mood or

anxiety disorder were found to be more likely to be diagnosed with cognitive impairment than those without psychiatric diagnoses (Weisbrot et al., 2014). Despite these findings, the relationship between cognitive impairment and mood in pediatric MS remains limited. Consequently, additional research is necessary to elucidate how mood symptoms develop over time and relate to other domains of functioning, like cognition and fatigue.

Disease-related clinical factors. Findings related to associations between disease-specific factors (e.g., time since onset, number of relapses, and disability status) and cognitive functioning in pediatric MS are inconsistent. For example, earlier onset of MS in children was found to be correlated with greater cognitive impairment, irrespective of physical impairment (Banwell & Anderson, 2005). MacAllister et al. (2005) also found that cognitive impairment correlated with time since onset, number of relapses, and disability level (i.e., Expanded Disability Status Scale [EDSS]) in a sample of pediatric MS patients. In contrast, other studies have found no correlation between time since onset, number of relapses, and disability status and cognitive functioning. Specifically, Amato et al. (2008) found that cognitive impairment did not correlate with time since onset or disability level (i.e., EDSS), in a sample of children with MS. Similarly, Amato et al. (2014) found no impact of disability level, time since onset, or number of relapses on participants' cognitive abilities across a 5-year, longitudinal study. Hosseini, Flora, Banwell, & Till (2014) found that younger age at disease onset in pediatric MS was associated with a greater likelihood of decline in performance on a measure of simple and complex attention and sequencing (i.e., the Trail Making Test, Part B) and a measure of motor-free processing speed (i.e., Symbol Digit Modalities Test). Contrary to these results, Holland et al. (2014) found that age of onset and time since onset were not significantly correlated with performance on neuropsychological measures of executive functioning in a sample of youth with

MS. Despite this lack of consensus, research has suggested that disease-related variables may play a role in the cognitive functioning of children with MS. Consequently, additional research is needed to clarify the impact of these factors in determining neuropsychological outcomes.

Transverse Myelitis

Prevalence and Demographic Factors

TM is a rare demyelinating condition, with approximately 1,400 new cases diagnosed in the United States per year (Berman, Feldman, Alter, Zilber, & Kahana, 1981). TM predominantly affects adults, with only around 20% of cases diagnosed prior to the age of 18 (Kerr, Krishnan, & Pidcock, 2005). However, it is important to note that TM emerges in a bimodal fashion, with peaks found to occur between the age ranges of 10 to 19 years and 30 to 39 years (Berman et al., 1981; Bhat, Naguwa, Cheema, & Gershwin, 2010; Jeffery, Mandler, & Davis, 1993; Christensen, Wermuth, Hinge, Bøemers, 1990).

The male-to-female prevalence ratio in pediatric TM is approximately 1.1 to 1.6:1 (Absoud et al., 2016); however, a preponderance of adolescent females diagnosed with TM have been identified in regions of the world at high risk for MS and Neuromyelitis Optica Spectrum Disorder (NMOSD), including the United States, Canada, Europe, and parts of Australia (Absoud et al., 2013; Alper, Petropoulou, Fitz, & Kim, 2011; Banwell et al., 2009; DaJusta, Wosnitzer, & Barone, 2008; Miyazawa et al., 2003; Pidcock et al., 2007; Thomas et al., 2012). Age distribution in pediatric TM also presents in a bimodal fashion, primarily impacting children under age 5 and older than age 10 (Deiva et al., 2015; Miyazawa et al., 2003; Pidcock et al., 2007). No racial or ethnic predisposition has been identified (Barnes et al., 2002).

Clinical Presentation and Etiology

Clinical presentation. TM is a rare, monophasic, immune-mediated demyelinating condition of the CNS caused by inflammation within the spinal cord. Furthermore, TM is a heterogeneous disorder with a vast spectrum of clinical presentations and outcomes (Krishnan, Kaplin, & Deshpande, 2004; Tavasoli & Tabrizi, 2018). This variability is due, in large part, to the potential for inflammation to occur at any particular level of the spinal cord, with more severe and debilitating outcomes often occurring when inflammation occurs at higher levels of the spinal cord. Despite this variability, TM is generally characterized by relatively acute onset of motor, sensory, and autonomic dysfunction, necessitating specialized, acute and longitudinal care (Deiva et al., 2015; Krishnan, Kaplin, & Deshpande, 2004).

While both MS and TM are CNS inflammatory demyelinating diseases, the inflammation in TM only occurs in the spinal cord, without obvious cerebral involvement. TM is also distinct from MS in that inflammation occurring in the spinal cord is the result of a single demyelinating event (Krishnan, Kaplin, & Deshpande, 2004). Historically, TM has been thought to primarily disrupt functioning in physical and sensory domains, resulting in much of the research focusing on symptoms related to these areas.

Research of the sequelae of pediatric TM is limited (Defresne et al., 2003); however, childhood manifestations of TM present in much the same way as adult manifestations of the disorder. Specifically, patients experience rapid onset of dysfunction in motor, sensory, and autonomic function (Deiva et al., 2015). Initial symptoms of TM in children are typically back pain, with rapidly progressing motor deficits in the lower extremities (Tavasoli & Tabrizi, 2018). Motor deficits are typically accompanied by flaccid paresis and decreased deep tendon reflexes (DTRs) upon examination; however, TM progresses to a state of increased tone and increased

DTRs below the level of spinal lesion during the subsequent days or months following initial symptom onset (Wolf, Lupo, & Lotze, 2012). A patient's upper extremities may also be impacted if the spinal cord lesion is in the cervical region (Wolf et al., 2012).

Sensory deficits and dysfunction are also present in pediatric TM. These sensory alterations can include pain, paresthesia (e.g., tingling, numbness, etc.), as well as bowel and bladder dysfunction (DeSena, Graves, Morriss, & Greenberg, 2014; Pidcock et al., 2007; Thomas et al., 2012). Autonomic dysfunction is another common symptom in pediatric TM, often manifesting as variations in body temperature and difficulty regulating respiration, as well as heart rate and rhythm (Wolf et al., 2012). These neurologic symptoms typically progress over the course of two to four days following symptom onset, and typically reach a nadir within five to six days of onset (Scott et al., 2011; Thomas et al., 2012; De Goede, Holmes, & Pike, 2010).

In 2014, there was a notable increase in the number of pediatric patients diagnosed with a relatively new subtype of TM, termed Acute Flaccid Myelitis (AFM; Absoud et al., 2016). AFM has been found to stem from a "polio-like" virus with outbreaks described in multiple regions of the United States (Aliabadi et al., 2016). AFM has garnered attention in the media, primarily due to the rapid onset and decline of children diagnosed with the condition, in addition to the rising number of confirmed cases (American Academy of Pediatrics [AAP], 2018; Centers for Disease Control and Prevention [CDC], 2018). However, AFM often results in more serious complications including disruption to nerves that control the head and neck, resulting in facial weakness, drooping of the eyelids, difficulty moving the eyes, as well as dysphagia and weakening of muscles involved in breathing, which can lead to respiratory failure (CDC, 2016; Messecar et al., 2016; Nelson et al., 2016). Characteristics such as asymmetric lower motor neuron-specific deficits and longitudinal anterior horn lesions of the spinal cord grey matter help

to distinguish AFM from other sources of acute flaccid paralysis, such as Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM), and TM (Messecar et al., 2016).

Etiology. Compared to MS, less is known about the etiology of pediatric TM. However, research has noted that a preceding infection or vaccination occurred within 30 days of diagnosis in 28% to 66% of children with TM (Pidcock et al., 2007; Thomas et al., 2012; Miyazawa et al., 2003). Other research has posited that mild spinal trauma, or vaccination (measles–mumps–rubella, hepatitis B, diptheria–tetanus–pertussis, influenzae, varicella, and small pox) may be preceding risk factors (Pidcock et al., 2007; Thomas et al., 2012). However, it is important to note that the cause of TM is often unknown in many cases. Such cases in which a cause cannot be identified are described as idiopathic (Krishnan et al., 2004).

As previously mentioned, identification of anti-MOG antibodies may help identify a potential mimic of MS (Reindl & Rostasy, 2015). As such, research has posited that identification of MOG antibodies in patients may assist with determining diagnosis, prognosis, and treatment of individuals with monophasic and recurrent demyelinating diseases (Reindl & Rostasy, 2015). Although there is currently limited information on how MOG antibodies are implicated in diagnosis and treatment of TM, it is important to note that research in this area is ongoing.

Pathogenesis, Diagnosis, and Treatment

Studies of TM pathology have revealed inflammation and neuronal loss in TM (Kerr & Ayetey, 2002). However, there is currently a dearth information on the immunopathogenesis of TM in children. Consequently, such studies in adults are often applied to children with TM. Krishnan et al. (2004) reported the focal infiltration of monocytes and t-cells in the spinal cords of adult patients with TM. Additionally, studies have observed demyelination and axonal loss on

imaging in both adults and children with TM (Awad & Stuve, 2011; Beh, Greenberg, Frohman, & Frohman, 2013). Despite these findings, the mechanisms of cellular and autoimmune responses that contribute to spinal cord inflammation and degeneration in children and adults remain unclear.

The diagnostic criteria for TM was established by the Transverse Myelitis Consortium Working Group (TMCWG). These criteria are applicable to adults as well as children with certain modifications that account for difficulties with delineating a sensory level in younger children (typically, children under 5 years of age; Absoud et al., 2016; Deiva et al., 2015; Thomas et al., 2012). Diagnostic criteria include the development of deficits in motor, sensory, and autonomic functioning that is attributable to the spinal cord; symptom progression to nadir between 4 hours and 21 days; bilateral, but not necessarily symmetric, signs and symptoms of dysfunction; a clearly-defined sensory level; a non-compressive lesion; and inflammation within the spinal cord, typically demonstrated by CSF pleocytosis or elevated IgG index (Tavasoli & Tabrizi, 2018).

Diagnosis is frequently made using MRI, which generally displays a long, centrally-located lesion (typically 3 to 4 segments) of T2 increased signal traversing more than two-thirds of the cross-sectional area of the spinal cord. Lesions may be contiguous or fragmentary (Barnes et al., 2002). Although gadolinium enhancement of the lesion is frequently observed, the absence of enhancement does not rule out TM (Tavasoli & Tabrizi, 2018).

Due to a lack of clinical trials, there are currently no FDA-approved therapies for treatment of TM in the acute phase. Consequently, medications used to treat TM are based on clinical experience and data obtained from open-label studies and retrospective analyses, and adult studies. With that being said, the standard therapy regimen for pediatric TM is high-dose

corticosteroids. Pediatric patients are frequently treated with 30 mg/kg/dose of intravenous methylprednisolone once a day for 3 to 5 days—a treatment regimen that has been found to be both safe and effective (Defresne et al., 2001). Specifically, a retrospective study found that children with TM who were treated with corticosteroids demonstrated improved short- and long-term outcomes compared to patients who did not receive steroid treatment (Defresne et al., 2001).

Plasma Exchange (PLEX) has been used to treat pediatric patients with TM. In adults, PLEX is often used to treat patients with moderate and aggressive forms of the condition, as well as in patients who have not demonstrated improvement following treatment with corticosteroids. Again, while there have not been any clinical trials conducted on the efficacy of PLEX in patients with TM, retrospective studies have found that patients treated with intravenous steroids followed by PLEX experienced a beneficial outcome (Bigi, Banwell, & Yeh, 2015; Llufriu et al., 2009).

Long-term treatment of residual symptoms such as those related to bowel and bladder dysfunction, pain, and spasticity are also important for TM patients. Considering this, bladder programs may be initiated with the addition of anticholinergic drugs such as oxybutynin or tolterodine (Tavasoli & Tabrizi, 2018). Pain symptoms are typically treated using medications like gabapentin, carbamazepine, phenytoin, amitriptyline or baclofen (Wolf et al., 2012). Pain is often associated with spasticity, which may be treated with flexible exercise routines, as well as bracing programs for joints, such as ankles, wrists, and/or elbows. Medication options (e.g., baclofen) for spasticity relief may be used in conjunction with such techniques, as well as botulinum toxin injections and/or serial casting (Tavasoli & Tabrizi, 2018; Wolf et al., 2012).

Neurocognitive Outcomes

Limited research has described the distinctive experiences of pediatric patients with TM from other children with demyelinating diseases (Pidcock et al., 2007; Trecker et al., 2009). Although Trecker et al. (2009) alluded to the presence of cognitive problems in children with TM, to date, there is only one published study seeking to describe cognitive functioning in pediatric TM (Harder et al., 2013). Harder et al. (2013) described cognitive deficits in a sample of 24 children diagnosed with TM. Of note, a subset of participants in this study were subsumed in the current project. Although group mean scores largely fell within the average range of functioning, observed deficits included impairments in verbal memory, attention, executive function, and processing speed. Most notably, the greatest deficits were observed in the areas of bilateral fine motor speed and dexterity, as well as visuomotor integration. Additionally, greater levels of impairment were found in attention and verbal memory domains when compared to processing speed and verbal fluency domains (Harder et al., 2013). Clearly, findings from Harder et al.'s (2013) study illuminate a risk for cognitive problems in pediatric TM. These findings raise important questions regarding the role of cerebral involvement in TM. Moreover, qualitative analyses conducted as part of Harder et al.'s (2013) study suggested that fatigue may play an important role in cognitive functioning in pediatric TM.

Psychosocial and Clinical Outcomes

Fatigue. To examine the role of other disease factors that may contribute to cognitive functioning in pediatric TM, Harder et al. (2013) examined rates of fatigue in a sample of children with TM. To assess fatigue symptoms in this sample, the PedsQL Multidimensional Fatigue Scale (PedsQL MFS) was administered to both patients and parents. The PedsQL MFS is a multidimensional scale that assesses fatigue symptoms across three domains: General (e.g.,

"Feeling tired," "Feeling physically weak (not strong)," etc.), Sleep/Rest (e.g., "Sleeping a lot," "Difficulty sleeping through the night," etc.), and Cognitive Fatigue (e.g., "Difficulty keeping his/her attention on things," "Difficulty remembering what people tell him/her," etc.). The PedsQL MFS provides a total fatigue score, in addition to producing scores for the three domains— General, Sleep/Rest, and Cognitive Fatigue—that comprise this total score. To examine fatigue as part of their study of neuropsychological functioning in a sample of children with TM, Harder et al. (2013) used the General and Sleep/Rest domains of the PedsQL MFS.

Results from Harder et al.'s (2013) study found that both parent-proxy report and self-report of general fatigue varied. Regarding parent-proxy report of general fatigue symptoms, mild levels of fatigue were observed in 33% of cases; whereas severe cases of general fatigue were observed in 52% of cases. Similarly, parent-proxy report of mild sleep-related fatigue was observed in approximately 43% of cases, with severe rates of sleep-related fatigue reported at approximately 29%. With regard to self-report of general fatigue, 14% of patients reported mild fatigue, and approximately 43% reported severe fatigue in this area. However, self-report of sleep-related fatigue revealed on mild concerns reported by 38% of patients.

As both parents and children endorsed significant levels of fatigue across both domains, Harder et al. (2013) suggested that fatigue may play a role in the cognitive problems observed based on a qualitative review of the data. As mentioned previously, fatigue is the most commonly reported symptom in both adults (Freal, Kraft, & Coryell, 1984; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Minden et al., 2006), and children (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005) with MS, and is also the most disabling symptom (Edgley, Sullivan, & Deboux, 1991; MacAllister et al., 2009; Smith & Arnett, 2005). Consequently, Harder et al.'s (2013) findings raise concerns related to the role of fatigue on cognition, quality

of life, and daily functioning in children with TM.

Mood. Research has yet to thoroughly examine the prevalence of mood problems in pediatric TM. However, a study has alluded to psychosocial functioning in pediatric TM. Trecker et al. (2009) surveyed the parents of 20 children (age range = 0.5-21) diagnosed with TM as part of an effort to understand the experiences of patients and families in navigating the healthcare system. To examine this question, the authors compared the percentage of specialty care services respondents reported their children were receiving to the percentage of reported desire for specialty services. Trecker et al.'s (2009) results found that respondents described satisfaction with current treatment services only 50% of the time. Respondents also expressed interest in receiving additional specialty in multiple domains. Specifically, 88% of respondents reported a desire to receive additional care from psychiatry. Such a finding may imply the need for psychological services in children with TM, warranting further evaluation of psychological functioning in this population.

As a component of their study investigating the cognitive functioning of children with TM, Harder et al. (2013) qualitatively explored clinical factors that may contribute to cognitive performance, including depression. Using a referral for further testing based on poor performance on a neuropsychological screening battery to indicate cognitive problems and parent-report of depression symptoms, the authors concluded that there was no clear relation between cognitive difficulties and depression symptoms in their sample. Despite these findings, additional research should be conducted to examine the relationship between depression and cognitive functioning in pediatric TM.

Disease-related clinical factors. Other than fatigue and mood (Harder et al., 2013), clinical factors, such as age at onset and physical functioning, and their relation to cognitive

functioning have yet to be explored in pediatric TM. However, despite mixed findings, the pediatric MS literature has suggested that earlier age at onset may be associated with greater cognitive dysfunction (Holland et al., 2014; Hosseini et al., 2014; MacAllister et al., 2005). Such results are perhaps unsurprising, as children with MS who experience early disease onset experience a disruption in typical CNS development during critical periods of brain maturation, physical advancement, and skill acquisition. Given that earlier disease onset also disrupts the typical CNS development of children with TM, in theory, earlier age at onset could contribute to cognitive difficulties akin to those observed in the pediatric MS literature. It has also been posited that delays in motor development in children with physical impairments, such as cerebral palsy, may result in limited interactions with or access to enriched (i.e., complex and variable) environments (Morgan, Novak, & Badawi, 2013). It has also been suggested that this limited exposure to enriched environments can impede cognitive development in children with CP (Morgan et al., 2013). Although support for this hypothesis is still emerging, such findings may have implications for pediatric TM patients, particularly those diagnosed at younger ages, given the potential for significant physical limitations in early development.

Summary

Recent research has found that children with CNS demyelinating diseases are at risk for cognitive impairment. Although MS and TM may be distinct in terms of disease-specific factors, such as pathogenesis, clinical presentation, diagnosis, course, and treatment, recent research suggests that these conditions may be comparable regarding neuropsychological and psychosocial functioning. Literature pertaining to pediatric MS comprises much of our current understanding of neuropsychological outcomes in youth with demyelinating conditions, with little emphasis on other conditions, such as TM. Moreover, less is known about disease-related

clinical factors (e.g., fatigue, depression, physical functioning, age at onset, and time since onset) that may contribute to neurocognitive outcomes. It is important for additional research to examine these factors to promote greater understanding of pediatric demyelinating diseases and identify areas of intervention. Consequently, the proposed study seeks to explore the role of fatigue, depression, and disease-related clinical variables (physical functioning, age at onset, time since onset) in determining the cognitive status (i.e., impaired or not impaired) in children with MS and TM.

CHAPTER THREE
Aims and Hypotheses

Overall Aim

To advance understanding of neuropsychological sequelae associated with pediatric demyelinating diseases by examining and comparing outcomes of MS and TM groups and exploring the relationship between clinical variables and cognitive status (i.e., impaired or not impaired).

Aim 1

Describe and compare symptoms of multidimensional fatigue (Sleep, Cognitive, and General) between MS and TM groups.

Hypothesis 1a: Based upon parent-proxy reports, youth with MS will be rated as having statistically significantly lower mean scores, reflecting worse fatigue symptoms, across domains on the PedsQL MFS as compared to youth with TM.

Hypothesis 1b: Youth with MS will demonstrate significantly higher proportions of elevated fatigue symptoms (i.e., mild and severe) per parent-proxy report than youth with TM.

Aim 2

Describe and compare symptoms of depression between MS and TM groups.

Hypothesis 2a: Based upon parent-proxy reports, youth with MS will be rated as having significantly greater mean scores, indicative of more depressive symptoms, based on the Behavior Assessment System for Children, Second Edition (BASC-2) Depression scale, as compared to youth with TM.

Hypothesis 2b: Based upon parent-proxy reports, youth with MS will be described as having significantly higher proportions of elevated depressive symptoms (i.e., At-Risk and Clinically Significant) than those with TM.

Aim 3

Determine if fatigue and/or depression, as well as other clinical variables, including diagnosis, age at onset, time since onset, and physical functioning contribute in determining cognitive status (i.e., impaired or not impaired) of youth with MS and TM. Cognitive status will be determined based on Huizenga et al.'s (2007) T^2 multivariate model for inferring cognitive impairment.

Hypothesis 3: Based upon parent-proxy reports, greater severity of fatigue symptoms and greater severity of depression symptoms, as well as diagnosis with MS, younger age at onset, longer disease duration, and poorer physical functioning will be significant predictors of cognitive impairment in youth with MS and TM.

CHAPTER FOUR
Materials and Methods

Participants

The current study is a retrospective analysis of data collected as part of ongoing research on pediatric demyelinating diseases approved by the Institutional Review Board (IRB) at the University of Texas Southwestern Medical Center and Children's Medical Center Dallas. Participant data was collected during routine visits to a specialty care clinic for pediatric demyelinating diseases at Children's Medical Center in Dallas, Texas. The present study sample was comprised of 67 participants with MS and 53 participants with TM (N = 120), ages 6 to18 years.

Participants were included if they had a diagnosis of MS/CIS or TM confirmed by a neurologist. As AFM is a subtype of TM and because both conditions involve pathology of the spinal cord, participants who were diagnosed with AFM were included in the TM group. Participants were excluded if they met criteria for ADEM or NMOSD; are known to be anti-MOG antibody positive; have been diagnosed with another neurologic condition (i.e., stroke, traumatic brain injury, epilepsy, brain tumor, or other unrelated neurologic problems); and/or have been on steroid treatment within 30 days of testing. While participants who were not proficient in English were excluded, it is important to note that participants who were proficient in English but had parents who spoke Spanish were included given the availability of language-appropriate parent-proxy measures.

Measures

Data collected included that derived from performance on standardized neuropsychological measures conducted as part of a cognitive screening battery, as well as parent report of fatigue, depression, and physical functioning obtained via standardized

questionnaires. Measure characteristics and psychometric properties are described in detail in Appendix A. Demographic and clinical information was also collected through a review of medical records as part of this retrospective review. Clinical information collected included diagnosis and age at symptom onset. Time since onset was calculated as the number of months between symptom onset and the date of assessment.

Planned Analyses

Prior to the analysis of data, a power analysis was conducted to determine an adequate sample size using $\alpha = .05$ and 1-Beta = .80. Assuming an effect size of d=.84, an estimated sample size of 50 for each group (100 total) is sufficient for detecting differences between groups using an independent samples t-test assuming equal group variances. The sample size estimate was performed using the Power Analysis and Sample Size Software (PASS) version 12.0 (Hintze, 2013).

Demographic and clinical data, including sex, handedness, age, race, ethnicity, caregiver primary language, age at onset, and time since onset were examined for between-group differences. Independent samples *t*-tests were used to examine age, age at onset, and time since onset; a chi-square test of independence, or if needed based on cell sizes, a Fisher's Exact test was used to examine categorical variables. If between-group differences are found, these variables will be included as covariates in subsequent analyses. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 23.0 (IBM, 2017). A probability value less than .05 will be considered statistically significant. Effect sizes will also be calculated to quantify the magnitude of difference in mean scores between MS and TM groups (i.e., the greater the effect size, the greater the difference between groups). Effect size guidelines for analyses examining differences between two means will be used (Coe, 2002; Tabachnick &

Fidell, 2014). Based on these guidelines, 0.2 will be considered a small effect, 0.5 will be considered a medium effect, and 0.8 will be considered a large effect (Coe, 2002; Tabachnick & Fidell, 2014).

Aim 1

To examine differences between pediatric MS and TM in the areas of fatigue, three independent samples *t*-tests were conducted to compare mean differences between MS and TM groups on parent-proxy reports of multivariate fatigue (i.e., Sleep, Cognitive, General). Effect sizes will be reviewed to examine the size of the difference between groups in parent-reported fatigue symptoms. To examine differences between pediatric MS and TM in frequency of fatigue symptoms by severity (i.e., normal, mild, and severe), a chi-square test of independence was used. Based on previous research (MacAllister et al., 2009) and the PedsQL normative data of healthy controls (Varni et al., 2002; Varni, Burwinkle, Szer, 2004), scores that are within 1 standard deviation (SD) below the mean or higher are considered normal while scores between 1 and 2 SDs below the mean are indicative of mild fatigue and scores that fall 2 or more SDs below the mean are considered to be indicative of severe fatigue.

Aim 2

To examine differences between pediatric MS and TM groups in the area of depression symptoms, an independent samples *t*-test was conducted to compare differences in means between MS and TM groups on parent-proxy reports of depression symptoms on the BASC-2. Effect sizes will be reviewed to examine the size of the difference between groups in parent-reported depression symptoms. To examine differences between pediatric MS and TM in frequency of depression symptoms by levels of severity, a chi-square test of independence, or if needed, a Fisher's Exact test was used. Based on the normative data of the BASC-2, parent-

reported depression symptom scores will be classified normal for scores less than 1 SD above the mean, At-Risk for scores between 1 and 2 SDs above the mean, and Clinically Significant for scores that are 2 or more SDs above the mean (Reynolds & Kamphaus, 2004).

Aim 3

To examine factors that may contribute to cognitive status in MS and TM groups, a Logistic Regression analysis was conducted to evaluate the impact of the proposed linear combination of independent variables in determining cognitive status (i.e., impaired or not impaired). The outcome variable of interest is classification of participants as cognitively impaired or non-impaired based on a binary, categorical model of cognitive impairment derived from Huizenga et al.'s (2007) T^2 multivariate model for inferring cognitive impairment using the cognitive measures in Table 11. The independent variables of interest include parent-proxy reports of fatigue (as measured by the General, Sleep/Rest, and Cognitive domains on the PedsQL MFS) and depression symptoms (as measured by the BASC-2 Depression scale). Parent-proxy reports of physical functioning (as measured by the PedsQL Generic Core Physical Functioning), age at onset, and time since onset were also entered as predictors in the logistic regression model. The logistic regression model was reviewed for the fit of the model to the data using the Hosmer-Lemeshow goodness-of-fit statistic; while non-significant *p*-values indicate adequate fit of the model to the data, *p* values between 0.2 to 0.4 indicate very good fit of the model to the data (Louviere, Hensher, & Swait, 2000).

CHAPTER FIVE
Results

Study Sample

A total of 127 subjects were reviewed for inclusion in the current study. Three participants were excluded given young age resulting in limited availability of standardized assessments, two were excluded due to neurologic diagnoses unrelated to their demyelinating condition, and two were excluded due to testing that revealed anti-MOG antibody seropositive status. Neuropsychological data were collected as part of routine clinical care, which involved standardized assessment of pediatric patients with demyelinating disorders. First assessment timepoint data was used for all participants except in one case when second assessment timepoint data was used given the participant's young age at the time of the initial evaluation. Of the final sample of 120 participants, 67 participants were diagnosed with MS/CIS, and 53 participants were diagnosed with TM. Within the MS/CIS group, 60 participants (88%) were diagnosed with MS; whereas, eight participants (12%) were diagnosed with CIS. Of these, five participants were subsequently diagnosed with MS, which was determined via medical record review.

Demographic Characteristics

Demographic characteristics of the study sample are detailed in Table 1. For the MS group, ages ranged from 7 to 18 years, with a mean of 15 years (SD = 2.5). Sixty-seven percent of MS participants were female, and 91% were right-handed. Mean time since onset was found to be 13.63 months (SD = 17.41; Range = 1-117), while mean age at onset was found to be 14.24 years (SD = 2.79; Range = 4-18). Regarding race, 63% reported that they were White, 21% as Black or African American, 3% as Asian, and 13% identified as Other. Pertaining to ethnicity, 63% identified as non-Hispanic, 33% as Hispanic or Latino, and 4% as Other. Ninety-six percent of caregivers' primary language was English.

In the TM group, ages ranged from 6 to 18 years, with a mean of 12 years (SD = 3.4;). Fifty-seven percent of TM participants were female, and 85% were right-handed. Mean time since onset was found to be 28.77 months (SD = 41.18; Range = 0-168), while mean age at onset was found to be 9.62 years (SD = 4.95; Range = 0-17). Concerning race, 79% identified as White, 8% as Black or African American, 2% as Asian, 2% as Native Hawaiian or Other Pacific Islander, and 9% as Other. Related to ethnicity, 66% identified as non-Hispanic, 25% as Hispanic or Latino, and 9% identified as Other. Ninety-three percent of caregivers' primary language was English.

Preliminary Analyses

Demographic and clinical data, including sex, handedness, age, race, ethnicity, caregiver primary language, time since onset, age at onset, and physical functioning were examined for between-group differences (Table 1). Chi-square analyses revealed no statistically significant differences between groups for sex ($\chi^2[n = 120] = 1.41$, $p = .24$) or handedness ($\chi^2[n = 120] = 1.09$, $p = .30$). Of note, due to violations of chi-square assumptions, a Fisher's Exact test was used for assessing differences between groups for race ($\chi^2[n = 120] = 6.45$, $p = .12$), ethnicity ($\chi^2[n = 120] = 3.49$, $p = .41$), and caregiver primary language ($\chi^2[n = 120] = .51$, $p = .70$). An independent sample *t*-test revealed that groups significantly differed by age ($p < .001$), time since onset ($p = .02$), age at onset ($p < .001$), and physical functioning ($p = .01$). Based upon these findings, time since onset and age at onset were considered as covariates for subsequent between-groups analyses; however, the tests for homogeneity of regression slopes for Analyses of Covariance (ANCOVA) were found to be nonsignificant across variables of interest (i.e., General, Sleep/Rest, and Cognitive fatigue, as well as depression). Therefore, these findings did not support the inclusion of covariates for examination in subsequent analyses.

Hypothesis 1

To compare symptoms of multidimensional fatigue (General, Sleep, and Cognitive) between MS and TM groups, three independent sample t-tests were conducted. Contrary to the hypothesis that youth with MS would be rated, per parent-proxy report, as having significantly more fatigue than those with TM, analyses revealed no differences between groups in mean scores: General (p = .84), Sleep/Rest (p = .06), and Cognitive fatigue (p = .05). Notably, however, mean scores for both MS and TM groups were at least 1 SD below the mean across domains (Table 2). Effect size calculations for comparison of parent-proxy reported fatigue symptoms between MS and TM groups were found to be consistent with a small to medium effect in General (d = *0*.38), Sleep/Rest (d = 0.36), and Cognitive (d = 0.40) domains (Coe, 2002).

To examine differences between pediatric MS and TM groups regarding proportions of subjects affected (Table 3), classified by severity (i.e., normal [less than 1 standard deviation below the mean], mild [between 1 and 2 standard deviations below the mean], and severe [2 or more standard deviations below the mean]), three chi-square tests of independence were performed. Contrary to the hypothesis that youth with MS will be rated as having significantly higher proportions of elevated fatigue symptoms (i.e., mild and severe) as compared to those with TM, results revealed no significant differences: General ($\chi^2[n = 111] = 2.67$, p = .29), Sleep ($\chi^2[n = 111] = 2.75$, p = .25), and Cognitive fatigue symptoms ($\chi^2[n = 111] = 5.12$, p = .08).

Percentages of elevated parent-proxy ratings of multidimensional fatigue symptoms were also calculated for MS and TM groups (Table 4). Regarding General Fatigue, severe fatigue was found for 56% of MS participants, and 47% of TM participants; whereas, mild fatigue was indicated for 10% of the MS sample and 20% of the TM sample. Concerning Sleep/Rest Fatigue,

parent-proxy ratings of severe symptoms were found for 45% of MS participants and 33% of TM participants. In contrast, mild Sleep/Rest fatigue was observed in 16% of participants with MS and TM alike. Parent-proxy ratings of severe Cognitive fatigue was found in 45% of MS participants, and 24% of the TM sample. Mild Cognitive fatigue was detected in 19% of youth with MS and in 29% of youth with TM.

Hypothesis 2

To compare the rate of depression symptoms between MS and TM groups, an independent sample t-test was conducted (Table 2). Results did not support the hypothesis that youth with MS would be described as having significantly greater mean scores of depressive symptoms than youth with TM, as there was no significant difference between MS and TM groups ($p = .56$). An effect size calculation for the comparison of parent-proxy reported depression symptoms between MS and TM groups was found to be trivial ($d = 0.11$; Coe, 2002).

To examine differences between pediatric MS and TM groups regarding proportions of subjects with elevated parent-proxy reported depression symptoms (i.e., normal [less than 1 SD above the mean], At-Risk [between 1 and 2 SDs above the mean], and Clinically Significant [2 or more SDs above the mean]), a chi-square test of independence was performed (Table 3). Results did not support the hypothesis that youth with MS would demonstrate higher proportions of elevated, parent-proxy reported depressive symptoms than youth with TM, as the chi-square test was not statistically significant ($\chi^2[n = 115] = .30$, $p = .90$).

Percentages of elevated (i.e., At-Risk and Clinically Significant) parent-proxy reported depression symptoms for MS and TM groups are detailed in Table 4. Parent-proxy ratings indicating At-Risk depression symptoms were found in 16% of the MS sample and 19% of the TM sample. Parent-proxy ratings of Clinically Significant depression symptoms were indicated

in 10% of the MS group and eight percent of the TM group. A total of 25% of the MS sample and 27% of the TM sample were rated as having elevated (i.e., At-Risk or Clinically Significant) depression symptoms, per parent-proxy report.

Hypothesis 3

Determination of cognitive impairment. Huizenga et al.'s (2007) T^2 mixture model was used to infer cognitive impairment for participants in both MS (n = 67) and TM (n = 54) groups. Data from standardized neuropsychological measures was entered into the model and included: CVLT-C/II Trial 1-5 Total; CVLT-C/II Trial 1; CVLT-C/II Trial 5; CVLT-C/II Long-Delay Free-Recall Trial; Grooved Pegboard dominant and non-dominant hand; Beery VMI and VP; Trail Making Test, Part A and B; WISC-IV/WAIS-III Digit Span and Symbol Search subtests; SDMT, Oral Version; D-KEFS Letter Fluency Test. See Table 5 for a list of measures used in the model with their descriptions.

To examine factors that may contribute to cognitive status for participants with MS and TM groups, a logistic regression analysis was conducted to evaluate the impact of a linear combination of variables of interest, including parent-proxy reports of fatigue, depression symptoms, and physical functioning, as well as diagnosis (i.e., MS or TM), age at onset, and time since onset. An assumption of a logistic regression is the linearity of independent variables. To test this assumption, each independent variable was examined for whether it was linearly related to the log of the outcome variable (cognitive status, based on the Huizenga et al. [2007] model). A preliminary logistic regression analysis was conducted, wherein the independent variables were included along with the interaction between each predictor and the log of itself (Tabachnick & Fidell, 2014). Results revealed that none of the interactions between the

predictors and log were significant, indicating that the main effects for each of the independent variables have not violated the assumption of linearity of the logit.

A binary logistic regression analysis was performed to ascertain the effects of multivariate fatigue (General, Sleep, Cognitive), depression, diagnosis (i.e., MS or TM), age at onset, time since onset, and physical functioning on the likelihood that participants meet criteria for cognitive impairment. The full model containing all predictors was found to be significant (Omnibus Test of Model Coefficients: $\chi^2 = 10.64$, $p = .03$), indicating that the model was able to distinguish between participants who were classified as cognitively impaired and those classified as non-cognitively impaired. Additionally, the Hosmer-Lemeshow goodness-of-fit statistic was indicated adequate fit of the model to the data ($p = .88$). However, none of the predictor variables in the logistic regression model were found to be statistically significant contributors to the likelihood that MS and TM participants are defined as cognitively impaired, or non-impaired, as shown in Table 6. Consequently, a stepwise logistic regression was performed to explore which of the variables of interest were contributors to the likelihood of cognitive impairment or non-impairment. Results of this stepwise logistic regression revealed that parent-proxy rating of depression symptoms was the only variable that contributed to the odds that participants are defined as cognitively impaired or not impaired. A review of the Odds Ratio statistic for the depression variable indicated that participants with greater parent-proxy reported depression symptoms were more likely to experience cognitive impairment (Table 7).

Exploratory Analyses

One sample *t*-tests (Table 8) were performed to determine if a statistically significant difference was observed between MS and TM sample means for multidimensional fatigue symptoms (General, Sleep/Rest, Cognitive) and the measure's mean (Standard Score = 100).

Results of this one-sample *t*-test revealed that youth with MS were rated as having a greater number of General ($p < .001$), Sleep/Rest ($p < .001$) and Cognitive fatigue ($p < .001$) symptoms as compared to the normative sample mean. Another one sample *t*-test was performed (Table 9) to determine if a statistically significant difference was observed between youth with TM and the measure's normative sample mean for multidimensional fatigue symptoms. Results of this one-sample *t*-test revealed that youth with TM were rated as having a greater number of General ($p < .001$), Sleep/Rest ($p < .001$) and Cognitive fatigue ($p < .001$) symptoms as compared to the normative sample mean. These results indicate that both youth with MS and youth with TM had significantly higher levels of parent-proxy reported multidimensional fatigue symptoms as compared to normative data. Likewise, large effect sizes were observed when comparing parent-proxy reported fatigue symptoms in youth with MS and the normative sample mean (General: $d = 1.15$; Sleep/Rest: $d = 1.01$; and Cognitive: $d = 0.98$; Coe, 2002). Similarly large effect size was observed when comparing parent-proxy reported fatigue symptoms in youth with TM and the normative sample mean for the General domain ($d = 1.06$), while effect sizes for the Sleep/Rest ($d = 0.79$) and Cognitive ($d = 0.61$) domains were found to be congruent with a medium to large effect (Coe, 2002).

Additional one sample *t*-tests were performed to determine if statistically significant differences existed in parent-proxy report of depression symptoms between the MS sample and the normative sample mean (T-Score = 50; Table 8), and between the TM sample and the normative sample mean (Table 9). The results of one-sample *t*-tests were found to be non-significant for MS ($p = .17$) and TM groups ($p = .41$), indicating that youth with MS and TM had similar levels of parent-proxy reported depression symptoms, as compared to the normative sample. Effect sizes for comparison of parent-proxy reported depressions symptoms in youth

with MS and the normative sample's mean (d = 0.17), as well as youth with TM and the normative sample's mean (d = 0.11), were both found to be trivial.

The difference between pediatric MS and TM groups based on cognitive status (i.e., proportions of subjects determined to be cognitively impaired versus non-impaired) were examined using a chi-square analysis (Table 10). Results from this analysis were found to be statistically significant ($\chi^2[n = 120] = 5.97$, $p = .02$), indicating a larger proportion of MS participants falling into the cognitive impairment group as compared to participants with TM. Specifically, 42% of participants with MS were classified as cognitively impaired while 21% of the TM sample were classified as cognitively impaired.

A chi-square analysis was conducted to examine differences between proportions of subjects with varying levels of parent-proxy reported fatigue (i.e., normal, mild, and severe) across multiple domains (i.e., General, Sleep/Rest, and Cognitive), and proportions of subjects defined as cognitively impaired or non-impaired. Results of chi-square analyses revealed that study participants were found to have significantly different proportions of General ($p = .03$) and Sleep/Rest fatigue ($p = .03$), such that participants with cognitive impairment were more likely to be rated as having severe General (68%) and Sleep/Rest fatigue (55%) than those without cognitive impairment. Though Cognitive fatigue was not found to be statistically significant ($p = .09$), 50% of participants with cognitive impairment were rated as having severe Cognitive fatigue symptoms (Table 11).

A Fisher's Exact test was performed to examine differences between proportions of participants who had varying levels of depression symptoms (Normal, At-Risk, and Clinically Significant) based on parent-proxy ratings and proportions of MS and TM subjects defined as cognitively impaired or non-impaired (Table 11). Results from this analysis were not statistically

significant (p = .12). Results suggest that groups who are classified as cognitively impaired versus non-impaired do not significantly differ in the proportion of classifications with elevated parent-proxy ratings of depression symptoms.

Percentages of elevated depression symptoms were also calculated for cognitively impaired and non-cognitively impaired to examine and describe differences (Table 11). For the cognitively impaired group, 32% of participants were found with elevated depression symptoms (i.e., at-risk or clinically significant), per parent-proxy report. In contrast, 23% of non-cognitively impaired participants were rated, per parent-proxy report, as having elevated depression symptoms. Although this analysis did not reveal significant differences between cognitively and non-cognitively impaired participants with regard to parent-proxy reported depression symptoms, cognitively impaired subjects had higher proportions of elevated depression symptoms than non-cognitively impaired subjects.

CHAPTER SIX
Discussion

Demographics

Regarding sample characteristics, the majority of both MS and TM samples were white (MS = 63%; TM = 79%) and non-Hispanic (MS = 63% and TM =66%). These findings are relatively consistent with known trends regarding the racial and ethnic composition of pediatric patients with MS (Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007; Banwell, Krupp, et al., 2007; Harbo, Gold, & Tintoré, 2013; Kennedy et al., 2006; Renoux et al., 2007), as well as more recent population-based research of incidence of MS in adults. Specifically, Langer-Gould, Brara, Beaber, & Zhang (2013) found that, between January 2008 and December 2010, White people comprised 52% of those diagnosed with MS, with Hispanic people diagnosed at 23%, Black people at 21%, and Asian or Other Pacific Islander at 3%. In contrast, because no racial or ethnic predisposition has been identified in pediatric TM, evaluating whether the sample under investigation for this project is representative of current racial and ethnic trends is difficult to discern (Barnes et al., 2002). Regarding sex composition, both MS (66%) and TM (57%) participants were mostly female, which is consistent with research suggesting that pediatric MS and TM are more common in females than males (Absoud et al., 2016; Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007; Banwell, Krupp, et al., 2007; Renoux et al., 2007; Chitnis et al., 2011; MacAllister et al., 2013).

Fatigue

Results revealed no significant differences in mean scores of multidimensional fatigue symptoms (General, Sleep, and Cognitive) between MS and TM groups. Similarly, groups did not differ in proportions (i.e., normal, mild and severe) of elevated fatigue symptoms, across domains (General, Sleep/Rest, or Cognitive). Although these findings do not provide support for

Hypothesis 1a or 1b, they suggest that both MS and TM groups are rated by parents as having comparable levels of fatigue symptoms and comparable proportions of elevated fatigue symptoms. Additionally, review of mean scores from parent-proxy report of multidimensional fatigue symptoms revealed scores below one or more SDs from the mean for both MS and TM groups. Moreover, exploratory analysis revealed that youth with MS and TM were rated as having a greater number of multi-dimensional fatigue symptoms than would be expected in healthy controls, which supports the trend in the literature regarding the prevalence of fatigue symptoms in pediatric MS (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005, 2009) and TM (Harder et al., 2013). As noted previously, the Harder et al. (2013) study sample is subsumed in the current study's cohort. These findings provide support for continued assessment and treatment of fatigue symptoms in pediatric demyelinating diseases. Additionally, these findings challenge the underlying assumption that brain-based biological factors (e.g., increased levels of proinflammatory cytokines and axonal loss) are the primary mechanism underlying fatigue in MS (Braley & Chervin, 2010). Unlike MS, the pathogenesis of TM does not entail obvious cerebral involvement and the condition is not recurrent. Therefore, notable and comparable levels of parent-proxy reported multidimensional fatigue observed in both MS and TM suggest that an additional or alternative mechanism(e.g., increased energy demand due to the increased muscular effort needed to compensate for spasticity and physical impairments; Braley & Chervin, 2010), which is shared by both groups may serve as a contributor to this observation. Consequently, additional research is necessary to explore other mechanisms which may be contributing to fatigue in MS and TM in order to improve understanding of these conditions as well as identify targets for interventions and treatment.

Pertaining to General fatigue symptoms, results from the current study revealed that MS and TM groups did not significantly differ based on mean scores or proportions of elevated symptoms. Even though results did not support that fatigue is a significant contributor to determining cognitive status in MS and TM, exploratory analyses revealed that those who were rated as having elevated fatigue symptoms are more likely to experience cognitive impairment than those without cognitive impairment. Notably, exploratory analyses also showed that youth with MS and TM were rated as having a greater number of General fatigue symptoms than would be expected in the general population. These findings are consistent with the current literature pertaining to the prevalence of parent- and self-report of fatigue symptoms endorsed via the PedsQL MFS in pediatric MS (Goretti et al., 2012; MacAllister et al., 2009), with rates of up to 73% (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005), which have also been associated with cognitive deficits (Goretti et al., 2012; Holland et al., 2014). As noted previously, the Holland et al. (2014) sample is included in the current study cohort. Although there are currently limited studies that have examined the prevalence of fatigue in pediatric TM, as a component of their study investigating cognitive functioning, Harder et al. (2013) found that fatigue was a prominent symptom (up to 52%) in youth with TM, and posited that fatigue may be associated with cognitive dysfunction. Findings from the Harder et al. (2013) study, as well as literature suggesting that fatigue is associated with deficits in various aspects of cognitive functioning in pediatric MS (Amato et al., 2008; Holland et al., 2014; MacAllister et al., 2005), taken together with findings from the current project, continue to raise concerns related to the impact of fatigue on cognition in youth with MS and TM.

Regarding Cognitive fatigue symptoms, though between-groups mean analyses did not reveal statistically significant differences in Cognitive fatigue (p = .05), it is important to note

that results approached significance, with the MS group showing greater cognitive fatigue than the TM group. These results are likely related to higher rates of cognitive impairment observed in MS versus TM as well as the pathogenesis of MS being a chronic inflammatory condition impacting the brain and spinal cord (Compston & Coles, 2008), as compared to TM, which is monophasic in course and believed to impact the spinal cord only (Krishnan et al., 2004). Additionally, it is important to note that means for both MS and TM samples were between 1 and 2 SDs below the mean, and exploratory analyses revealed a greater number of cognitive fatigue symptoms than would be expected in healthy controls for both groups. This finding is perhaps surprising given that TM is a disease that impacts the spinal cord only without obvious cerebral involvement (Krishnan et al., 2004; Harder et al., 2013); however, it is important to note that fatigue is often reported in children with other chronic illnesses (e.g., cerebral palsy, neuromuscular diseases, epilepsy, rheumatological conditions; Berrin et al., 2006; Lai et al., 2012; Montes et al., 2013) and adults with other neurological illnesses (e.g., Parkinson disease, traumatic brain injury, stroke, etc.), which involve physical impairments (Kluger, Krupp, & Enoka, 2013), and often impact multiple domains of functioning (e.g., physical and cognitive functioning; Benito-León, Manuel Morales, Rivera-Navarro, & Mitchell, 2003). Moreover, physical fatigue can have an impact on mental functioning and vice versa (DeLuca, 2005). In a sample of youth with MS, Holland et al. (2014) found that both parent- and self-report of general fatigue (i.e., feelings of tiredness and weakness) were correlated with performance on a motor-based, executive functioning task.

It is important to note that while significant differences were not observed between MS and TM groups in the Sleep/Rest fatigue domain, results approached significance ($p = .06$). While there is some literature to suggest that youth with MS experience fewer sleep-related

problems than healthy controls (Sikes, Motl, & Ness, 2018; Zafar, Ness, Dowdy, Avis, & Bashir, 2012), other research has suggested that approximately two-thirds of parents of children with MS, and over a quarter of pediatric patients with MS report at least mild sleep problems and associated fatigue (MacAllister et al., 2009). Despite inconsistent findings in the current literature, the present study revealed that caregivers of youth with MS describe sleep-related fatigue as a notable issue for their children. There is limited literature regarding sleep-related fatigue in pediatric TM. Harder et al. (2013) described proportions of fatigue (General, Sleep/Rest) in a sample of children with TM using the PedsQL MFS given to parents of youth with TM. The authors found that parents endorsed noteworthy proportions of fatigue (mild = 42.9%, severe = 28.6%) in the Sleep/Rest fatigue domain. It is important to note that a subsample of participants that were used in Harder et al.'s (2013) study were subsumed in the current study. Even though the rate has decreased somewhat, continuing the trend observed in the Harder et al. (2013) study with a larger TM sample size, results from the current project revealed that participants with TM were rated as having notable Sleep/Rest fatigue (mild = 16%; severe = 33%).

Depression

There were no significant mean differences between pediatric MS and TM samples in parent-proxy reported depression symptoms or proportions of elevated depression symptoms (i.e., At-Risk and Clinically Significant). Consequently, these findings did not support Hypothesis 2a or 2b. Results suggest that MS and TM groups were rated as having relatively similar levels of depression symptoms. Taken together with exploratory analyses, findings from the current project indicate that MS and TM groups do not significantly differ in terms of

severity of symptoms, proportion of elevated depression symptoms, nor do group mean scores significantly differ from normative data.

Interestingly, study results revealed that depression was the only variable of interest that significantly contributed to cognitive status as discussed below. Youth with MS and TM were reported to experience elevated depression symptoms (i.e., At Risk or Clinically Significant) at proportions of 25% and 27%, respectively. Importantly, while the current study evaluated symptoms rather than diagnoses, proportions of elevated depression symptoms observed in MS and TM participants are relatively consistent with other research which has proffered that depressive disorders occur at a rate of about 27% in children with demyelinating diseases (Weisbrot et al., 2010). Though research shows that pediatric patients with MS meet criteria for affective disorders (e.g., depressive disorders, anxiety disorders, etc.) at a rate of approximately 31% to 46%, of those, only an estimated 15% meet criteria for a depression diagnosis (Goretti et al., 2012; MacAllister et al., 2005). Regarding TM, research has yet to thoroughly examine the prevalence of mood problems in this population; however, the trend observed in Harder et al. (2013; sample subsumed in the current study), which identified approximately 30% of TM subjects with elevated depression, while slightly lower, generally continues to be seen in the larger sample size of the current study. Trecker et al. (2009) found that 88% of parents of pediatric TM patients reported a desire to receive care from psychiatry, implying the general need for mental health services in children with TM.

Notably, the proportion of elevated depression symptoms endorsed by both MS and TM participants is somewhat higher than current prevalence estimates of depression in children and adolescents with other complex medical issues such as diabetes (up to 18%) and heart disease (up to 23%; Katon, 2011). Taken together with current findings that more depression symptoms

contribute to the likelihood of cognitive impairment, results support routine screening and evaluation of depression symptoms to direct appropriate intervention (e.g., medication and psychotherapy). Additional research is necessary to continue to describe rates of mood-related symptoms in pediatric demyelinating disorders as well as to explore the relationship between depression and cognitive functioning in pediatric MS and TM.

An additional consideration that warrants attention is the role of disease-related neurological factors that have been implicated in depression in MS. Specifically, research has suggested that depression in MS is biologically mediated by some of the processes involved in the immunopathogenesis of the condition, such as the presence of proinflammatory cytokines, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and lesion location (Feinstein et al., 2004; Pucak, Carroll, Kerr, & Kaplin, 2007). Importantly, the aforementioned neurological factors are notably absent in pediatric TM. As such, findings of elevated depression symptoms in TM, similar to those observed in MS, may represent an alteration in mood that is not accounted for by obvious brain-based, immune-mediated damage. Consequently, findings from the current study, indicating comparable levels of elevated parent-proxy reported depression symptoms (MS = 25%, TM = 27%), challenge the underlying assumption that neurologically-related biological factors are the primary mechanism contributing to depression in MS (Pucak et al., 2007). Thus, additional research is needed to examine additional mechanisms which could be contributing to depression symptoms in both MS and TM to increase understanding of these conditions and improve upon targeted interventions and treatment protocols.

Predicting Cognitive Status

Contrary to our hypothesis, findings from the binary logistic regression revealed that none of the variables of interest, including depression and fatigue, were significant contributors

to cognitive status (i.e., impaired or non-impaired) in youth with MS and TM; however, a stepwise logistic regression showed that parent-proxy ratings of depression symptoms were found to be the only predictor variable that contributed to the likelihood that MS and TM participants will be identified as cognitively or non-cognitively impaired. Such findings are consistent with extant literature, which has suggested that emotional dysfunction (depression, anxiety) is associated with poorer performance on cognitive measures (Holland et al., 2014; Julian & Arnett, 2009). Moreover, these findings are consistent with a robust literature that has identified deficits in various cognitive domains (e.g., executive functioning, attention, memory and processing speed) in children and adults with depression (Blanken et al., 2017; Hammar & Årdal, 2009).

However, the results of the logistic regression and stepwise logistic regression, indicating that fatigue does not play a significant role in determining the cognitive status of youth with MS or TM is mostly inconsistent with extant literature, which has suggested that fatigue is associated with cognitive dysfunction in pediatric MS (Charvet et al., 2016; Holland et al., 2014; Julian & Arnett, 2009; Weisbrot et al., 2014), and research which has implicated fatigue as a contributor to cognitive dysfunction in pediatric TM (Harder et al., 2013). Despite the results of the logistic regression analysis indicating that fatigue did not play a role in determining the cognitive status of youth with MS and TM, exploratory analyses revealed that cognitively impaired participants were significantly more likely to experience elevated General and Sleep/Rest fatigue than their non-cognitively impaired counterparts. Yet, interestingly, neither Cognitive fatigue nor depression was found to be statistically significant based on cognitive status (impaired vs. non-impaired). That said, percentages of elevated depression symptoms were higher than would be expected considering findings regarding depression in other pediatric complex medical

conditions (Katon, 2011). Taken together, results from the present study suggest that it continues to be important for clinicians to screen for both fatigue and depression in pediatric patients with MS and TM in order to determine if interventions (e.g., educational supports, medication, therapeutic intervention, etc.) are warranted. Doing so may assist in supporting cognitive functioning in youth with MS and TM.

Logistic regression results also revealed that none of the other clinical factors (i.e., age at onset with demyelinating disease, time since disease onset, or physical functioning) significantly contributed to the likelihood that MS and TM participants would be identified as cognitively or non-cognitively impaired. These findings are somewhat consistent with the current literature in pediatric MS, as some studies have suggested no correlation between time since disease onset, number of relapses, and disability status and cognitive functioning (Amato et al., 2008, 2014; Holland et al., 2014), while others have suggested such factors are associated with cognitive deficits (Hosseini et al., 2014). Regarding pediatric TM, this is the first known study to examine age at onset with demyelinating disease, time since disease onset, and physical functioning on cognitive functioning. Thus, findings from the current project support the notion that disease-related clinical factors may have a limited role in determining the cognitive status of youth with MS, as well as TM. However, given mixed findings in the pediatric MS literature, as well as limited research on the role of these disease-related clinical variables and cognitive functioning pediatric TM, additional research is needed to clarify the impact of these factors in determining neuropsychological outcomes in both of these populations.

Findings from an exploratory analysis found that MS and TM groups significantly differed in cognitive impairment classifications. Specifically, 42% of participants with MS were classified as cognitively impaired, whereas, 21% of TM subjects were classified as cognitively

impaired. For the MS group, these results are somewhat inconsistent with the current literature, which has identified neurocognitive impairment in about one-third of patients with pediatric MS (Amato et al., 2008; Julian et al., 2013). Indeed, findings from the current study indicating 42% of participants with pediatric MS were classified as cognitively impaired are more in line with the adult MS literature, which has estimated that cognitive impairment occurs in 40 to 60% of patients (Rao, Leo, Bernardin, & Unverzagt, 1991). Therefore, results from the present study suggest that more participants with MS experience cognitive impairment than previously estimated.

As mentioned previously, studies drawing conclusions relative to cognitive impairment have employed various methods, such as composite scores or number of individual subtest cutoff scores, that may present empirical problems (Tan et al., 2018). Because research has documented deficits in multiple cognitive domains (intellectual functioning, attention and executive functioning, visuomotor and visuospatial functioning, language, and memory; Blaschek et al., 2012; MacAllister et al., 2013; Suppiej & Cainelli, 2014), the current study employed a multivariate statistical analysis (Huizenga et al., 2007) in an attempt to improve upon the previous methodology used to define cognitive status in clinical research. Considering that this multivariate model may improve upon other forms of inferring cognitive status, it is possible that the greater rates of cognitive impairment observed in the current study are a more accurate reflection of rates of cognitive impairment in children with MS and are more consistent with rates of cognitive impairment in adults. Thus, it continues to be important for clinicians to screen for cognitive concerns in youth with MS in order to assist with intervention. However, because cognitive impairment is multidimensional in nature, it is important for clinicians and researchers to survey multiple domains of neurocognitive functioning and consider utilizing a multivariate

analysis for determining cognitive impairment when working with patients with MS and TM.

Although results from the current project clearly indicate that pediatric patients with MS are at greater risk for experiencing cognitive impairment than their TM counterparts, it is important to note that approximately 21% of TM participants were identified as cognitively impaired. These findings are relatively consistent with rates of cognitive impairment in other pediatric demyelinating conditions, such as 18% of those with CIS (Julian et al., 2013) and 22% of ADEM patients (Beatty et al., 2016). It is important to note that the pathogenesis of pediatric CIS and ADEM both involve autoimmune inflammatory, demyelinating events that affect the brain and spinal cord; whereas, the pathogenesis of TM involves a single autoinflammatory 'attack' that affects the spinal cord only. Consequently, results from the current study posit that despite the monophasic nature of the condition, youth with TM experience of cognitive impairment at a rate similar to youth with other demyelinating diseases, including those which are recurrent in nature and include cerebral involvement. Given this finding, it is important for clinicians to screen for cognitive problems in pediatric TM, as well as pediatric demyelinating disorders with obvious brain-based pathology, in order to determine if impairment is present to direct targeted interventions (e.g., the implementation of academic intervention plans, medication, therapeutic intervention, etc.).

Limitations and Future Directions

A limitation of the current study is the modest sample size; however, it is important to note that MS and TM are considered rare conditions, with pediatric manifestations of these diseases comprising a small subset of those affected. Additionally, power analyses were conducted using conservative estimates for MS and TM sample sizes (n = 50 for each group; total of 100 participants) to ensure adequate power and limit violations of statistical assumptions

(Tabachnick & Fidell, 2014). Results of this power analysis indicated sufficient power for detecting differences between groups using independent samples *t*-tests. Additionally, sample sizes for both MS (n = 67) and TM (n = 53) groups were greater than the conservative appraisals utilized in the a priori power analysis, suggesting sufficient statistical power for detecting differences between groups than initially estimated. Nevertheless, statistical power may still may not have been ample enough to detect all significant findings. Consequently, future research would likely benefit from increased sample sizes, which may be best accomplished via multi-site studies.

Another limitation of the current study was that certain clinical variables were not available for analysis. Such clinical variables may include the number of relapses experienced by MS participants, the number of participants being treated with DMTs, and the number of participants being treated with pain or spasticity medications. As such, the impact of such factors on fatigue, depression, and/or cognitive status remains unknown. Future research should consider the impact of additional clinical variables, such as those noted above, on the cognitive and psychosocial status of children with demyelinating conditions.

The current study was limited given the use of only a single individual, parent-proxy report scale for assessing depression symptoms (i.e., the BASC-2 Depression subscale). To further evaluate the presence of depression symptoms in youth with MS and TM, the use of other standardized parent-proxy measures (e.g., Children's Depression Inventory, Second Edition [CDI-II]) may help to more thoroughly assess for the depression symptoms. Given that parent- and self-report of internalizing symptoms may differ, the use of a standardized self-report depression measure (e.g., BASC-2 or BASC-3 self-report, CDI-II, self-report version; Beck Depression Inventory, Second Edition) may also help clarify the presence of depression

symptoms in addition to providing an opportunity for researchers examine discrepancies in parent- and self-report of symptoms. Furthermore, the use of an additional measure that emphasizes diagnostic criteria (e.g., Kiddie Schedule for Affective Disorders and Schizophrenia [K-SADS],) or other diagnostic clinical interview, could also be used in place of rating scales, and may elucidate the presence of a depression diagnosis (e.g., Major Depressive Disorder) rather than providing ratings of a sample of symptoms only.

Another limitation of the current project was that depression was the only mood-related variable examined. As research has suggested that individuals with MS are at-risk for multiple psychological difficulties (Goretti et al., 2010; MacAllister et al., 2005, 2013; Weisbrot et al., 2010), it may be important for future research to examine additional psychological factors (e.g., anxiety, adjustment-related symptoms, etc.) with respect to their impact on cognitive functioning in youth with MS and TM. Again, this could be accomplished via the administration of standardized parent- and self-report measures of psychosocial functioning targeting domains of interest (e.g., the Multidimensional Anxiety Scale for Children, Second Edition [MASC-2], parent- and self-report).

Importantly, research has found that caregivers and their children often differ in their perceptions of functioning in psychosocial domains (e.g. social, emotional and school experience), in diagnostic symptomatology (e.g., ADHD), and health-related quality of life (Galloway & Newman, 2017; Marques et al., 2013; Upton, Lawford, & Eiser, 2008). Some of this research has even found that children may underestimate their degree of functional impairment, particularly at school (Marques et al., 2013). Given such concerns regarding accuracy of reporting, as well as statistical limitations caused by modest sample sizes for both MS and TM groups, the current project relied solely on parent-proxy report of multidimensional

fatigue, depression, and physical functioning symptoms. Future research may benefit from use and analysis of both parent-proxy and self-report measures across multiple areas to more comprehensively evaluate psychosocial functioning in pediatric patients with demyelinating conditions.

The current study was also limited by a lack of information regarding the number of MS and TM participants who were undergoing treatment or had been treated for fatigue and/or depression symptoms. Understanding the relation between treatment and symptoms would provide valuable information regarding effective therapies for fatigue and depression, as well as an additional consideration when examining rates of fatigue and depression in pediatric MS and TM. Consequently, future research should consider the role of treatment when examining the presence of clinical symptoms, such as depression and fatigue.

Research has just recently begun to examine the impact of factors such as self-compassion and resilience on health-related quality of life in individuals with MS. Specifically, a couple of studies have indicated that self-compassion and resilience may help adolescents and young adults with MS manage their medical condition and cope with their challenges, as well as overcome stress and increase quality of life (Rainone et al., 2017; Nery-Hurwit, Yun, & Ebbeck, 2018). Though beyond the scope of this study, future research should explore how such factors may contribute to outcomes (e.g., health-related quality of life, mood, adjustment, etc.) in children with MS and TM and other demyelinating conditions.

The use of an abbreviated neuropsychological battery that did not utilize a stand-alone intellectual quotient (IQ) measure or investigate all domains of neurocognitive functioning was an additional limitation of the current project. As neuropsychological performance data was collected as a component of participants' visit to a multidisciplinary, specialty-care clinic,

screening evaluations were necessarily brief (approximately 60 minutes in length). Consequently, evaluation of participants' neuropsychological functioning was limited to those measures which targeted areas that may be especially vulnerable to CNS demyelinating conditions (Charvet et al., 2014; Charvet et al., 2017; MacAllister et al., 2013; Portaccio et al., 2009). Furthermore, surveying multiple domains of neuropsychological functioning rather than relying on a stand-alone, or abbreviated IQ measure, likely served to provide a wide-ranging assessment of overall cognitive functioning. It is also important to note that research has suggested that IQ is not central to determining cognitive impairment (Kuntsi, Wood, Van Der Meere, & Asherson, 2009; Wood et al., 2012). With such caveats in mind, when feasible, future research may benefit from a more comprehensive assessment approach to control for IQ and investigate neuropsychological functioning in additional cognitive domains (e.g., visual memory, language, other facets of executive functioning, as well as academic achievement).

Future studies may also benefit from the use of an additional means of verifying whether determinations about participants' cognitive status, made via multivariate statistical models, are consistent with clinical interpretations of cognitive assessment. One method for such verification is the use of clinician judgment in corroborating the cognitive status of participants. For example, clinicians could indicate whether or not the participant "failed" the screening and was referred for more testing as a marker for impairment that incorporates clinical judgement. Using clinician judgment to validate statistical methods for determining cognitive impairment would allow for integration of multiple sources of information (e.g., patient history, performance on cognitive tests, academic achievement, etc.) routinely used to make determinations about neuropsychological functioning in the clinical setting.

Although outside of the scope of this project, there is an emerging literature investigating the association between neuroanatomical findings and neuropsychological outcomes in pediatric demyelinating diseases. In pediatric MS, studies have established that imaging findings, including the mid-sagittal plane of the corpus callosum area, thalamic volume, whole brain and regional brain volume, as well as lesion volume are associated with neurocognitive deficits in pediatric MS (Till et al., 2011; Till, Ho, et al., 2012; Till et al., 2013). However, to date, no such studies have been conducted in pediatric TM. Such studies may both increase understanding of neuroanatomical differences in pediatric TM, as well as provide another means for identifying cognitive risk factors. Therefore, future research would not only benefit from conducting additional imaging studies in pediatric MS, but also by investigating potential relationships between imaging and neuropsychological findings in pediatric TM.

Acknowledgements

The authors would like to acknowledge the patients and families who contribute to advances in the understanding of pediatric demyelinating diseases.

APPENDIX A
Measures

See Table 11 for a summary of the neuropsychological measures included in the multivariate analysis to determine cognitive impairment. Names and descriptions of measures, as well as the scales used to assess performance on measures (e.g., Standard Scores, Scaled Scores, T-Scores) are provided in the table. Means and standard deviations of scales are also provided.

Neuropsychological Functioning

A neuropsychological screening battery was administered to participants, designed to assess multiple domains of cognitive functioning that are commonly impacted by demyelinating diseases. There were slight variations in the measures administered to participants based on participant age given available age-based normative data for each measure. Age ranges of measures administered to participants are listed by test below.

Verbal learning and memory. Verbal learning and memory were assessed using the California Verbal Learning Test, Children's Version (CVLT-C; 5–16 years) and CVLT, Second Edition (CVLT-II; 17–18 years). The CVLT-C/II is a measure designed to assess verbal learning, recall and recognition. Patients receive a list of 15 words in the form of a shopping list for a specific day of the week (List A), which the patient is then asked to recall. This process is repeated a total of 5 times. Administration of this first list is followed by the administration of a second, interference list (List B). After the administration of List B, the patient is then asked to freely recall List A, as well as recall List A when given semantic cues. Following a 20-minute delay, during which time a non-verbal test is administered, a long-delay free recall and long-delay cued recall of List A are initiated. A final test is administered to assess the patient's recognition of words that were administered on List A. Results from this measure include several different scores including total recall, learning slope (i.e., whether more items were consistently

learned and retained across repeated trials), interference, retention over short and long delays, among others (Delis, Kramer, Kaplan, & Ober, 1994; Delis, Kramer, Kaplan, & Ober, 2000). Standardization of the CVLT-C was based on samples of healthy 560 children for ages 5 to 12 range and 280 children for ages 13 to 16. Norms were stratified by age, sex, race, and parental education to be consistent with 1988 U.S. Census (Delis et al., 2000). Standardization of the CVLT-II was based on a sample of 1,087 healthy adults ages 16 to 89. Norms were stratified by age, sex, race, and parental education to be consistent with 1990 U.S. Census (Delis et al., 1994).

Internal consistency and alpha reliabilities for the CVLT-C are generally above .80 in a sample of healthy children and children with clinical conditions (e.g., developmental, medical, and psychiatric conditions; Delis et al., 2000). Similarly, alpha reliability results for the CVLT-II ranges from .80-.96 in a sample of healthy adults and adults with developmental, medical, and psychiatric conditions (Delis et al., 1994). Both the CVLT-C and CVLT-II have been used to evaluate learning disabilities, attention-deficit/hyperactivity disorder (ADHD), traumatic brain injury, intellectual disability, and other neurological disorders (Delis et al., 1994; Delis et al., 2000).

Auditory attention and working memory. Auditory attention and working memory were assessed using the Digit Span subtest from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; 6–16 years; Wechsler, 2003) and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; 17–18 years; Wechsler, 1997). The WISC-IV and WAIS-III are both comprehensive tests of intelligence for children and adults respectively. The normative sample for the WISC-IV included 2,200 English-speaking U.S. children from 6 years to 16 years 11 months and stratified according to the 2000 U.S. Census (Wechsler, 2003). The normative

sample for the WAIS-III included 2,450 English-speaking U.S. adults from 16 years to 89 years and stratified according to the 1995 U.S. Census (Wechsler, 1997).

On both the WISC-IV and WAIS-III, the Digit Span subtest is comprised of two tasks: Digit Span Forward, in which patients are asked to recall a sequence of numbers in the same order; and Digit Span Backward, in which the child is asked to recall a sequence of numbers in the reverse order. This subtest is designed to measure working memory, mental manipulation, cognitive flexibility, encoding, rote verbal memory and learning, as well as attention (Wechsler, 1997, Wechsler, 2003). In a sample of healthy individuals and individuals with clinical conditions, the reliability of the WISC-IV Digit Span subtest is .87; whereas, the reliability of the WAIS-III Digit Span subtest is .82 in a sample of healthy individuals and individuals with clinical conditions (Wechsler, 1997, Wechsler, 2003).

It is important to note that a subset of participants (18 MS and 10 TM participants) who were evaluated in 2016 or later were administered the Digit Span subtest from the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V; Wechsler, 2014), and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008). Given that the normative data of the Forward and Backward trials of the WAIS-IV and WISC-V are not separated based on these trials alone, a mean of the scaled scores for the Forward and Backward trials was used as a replacement for the total score, in order to maintain consistency with participants who were administered the WISC-IV and WAIS-III.

Processing speed. Speed of processing information was evaluated using both a motor-based and motor-free metric of assessment. Motor-based processing speed was assessed using the Symbol Search subtest from the WISC-IV/WAIS-IV. The Symbol Search subtest requires that patients scan and search a series of symbols and match them to a target group of symbols

within a specific time limit. This subtest is designed to measure processing speed, short-term visual memory, visual discrimination, visual-motor integration and coordination, and cognitive flexibility (Wechsler, 1997, Wechsler, 2003). The reliability of the WISC-IV Symbol Search subtest is .84; whereas, the reliability of the WAIS-III Symbol Search subtest is .88 in a sample of healthy adults and adults with clinical conditions (Wechsler, 1997, Wechsler, 2003).

The Symbol Digit Modalities Test (SDMT; 8-18 years), Oral Version was used to assess motor-free processing speed. The SDMT is a brief, timed task of speeded information processing. The task requires patients to use a visual reference key to pair numbers with specific symbols using a verbal response. Similar to the WISC-IV/WAIS-IV Symbol Search subtest, the SDMT subtest is designed to measure processing speed, short-term visual memory, visual discrimination, and cognitive flexibility without a motor demand (Smith, 1982). The SDMT has been utilized in numerous patient populations, including individuals with traumatic brain injury, learning problems, mood disorders, and other various neurological disorders. Most importantly, the SDMT has been used in research of patient populations with motoric difficulties, including children with MS and TM (Amato et al., 2008, 2010, 2014; Harder et al., 2013; Holland et al., 2014; Till et al., 2011, 2013). In a sample of healthy children and adults, the reliability of the SDMT, Oral Version is .76 (Smith, 1982).

Visual-motor integration and visual perception. Visual-motor integration and visual perception were examined using the Beery Developmental Test of Visual-Motor Integration, Sixth Edition (VMI-6; 2–18 years). Normative data for children ages 2 years to 18 years included 1,737 children, stratified by demographic factors, including participant age, gender, residence (urban vs. rural), ethnicity, and parental education to be consistent with 2010 U.S. Census data. While children with disabilities were included in the normative sample, the test manual does not

provide details regarding the nature of the disabilities of participants or the number of representative individuals in the sample (Beery & Beery, 2010).

The VMI requires patients to copy increasingly-complex geometric forms using a pencil and paper. This task is designed to assess a patient's visual-motor integration abilities. The reliability of the VMI-6 in a sample of healthy children and children with clinical conditions (e.g., developmental and medical conditions) ranges from .79 to .89, depending on age group, with an average reliability of .88 for children between the ages of 2 and 17 years (Beery & Beery, 2010).

The VMI-6 also contains an optional measure of motor-reduced visual perception: The VMI-6 Supplemental Developmental Test of Visual Perception (VP). Patients' performance on the VMI can be contrasted with their performance on the VP, which may assist clinicians and researchers with discriminating between patients who have disturbances of visual-perception or motoric difficulties (Beery & Beery, 2010). The reliability of the VP in a sample of healthy children and children with clinical conditions ranges from .74 to .87, with an average reliability of .81 for children between the ages of 2 and 17 years (Beery & Beery, 2010).

Fine-motor speed and dexterity. Bilateral fine-motor speed and dexterity were assessed using The Grooved Pegboard (5–18 years). The Grooved Pegboard is a board that contains twenty-five holes with differently-positioned slots, and pegs which have a groove along one side. Pegs must be rotated so that the grooved edge of the peg matches the hole before they can be inserted. Patients are asked to place these pegs into the holes of the board using one hand at a time. This task is designed to assess bilateral fine-motor speed and dexterity. Moreover, examining motor performance on both sides of the body allows for the interpretations of lateralized brain impairment or damage (Lafayette Instrument, 2002). Normative data by Knights

and Moule (1968), adapted from Baron (2004) indicate that test-retest reliability coefficients for a sample of healthy children ages 5 to 18 range from marginal (.67) to high (.86).

Attention. Simple and complex attention and sequencing were assessed using the Trail-Making Test (TMT; 9–18 years). The TMT is a measure of visual attention and cognitive flexibility (i.e., task-switching), consisting of two parts: Part A (TMT-A) wherein the patient is asked to sequentially connect 25 numbered dots as quickly and accurately as possible; and part B (TMT-B) wherein the patient is asked to connect the dots, alternating between numbers and letters (i.e., 1, A, 2, B, 3, C, etc.) as quickly and accurately as possible. This task is designed to assess aspects of executive functioning, including visual attention, processing speed, scanning, and cognitive flexibility. The reliability of the TMT-A task is .74, and the reliability of the TMT-B is .84 in an adult population (United States Army Individual Test Battery, 1994).

Verbal fluency. Verbal fluency was assessed using the Letter Fluency subtest from the Delis-Kaplan Executive Function System (DKEFS; 8-19 years). The DKEFS is a test consisting of nine stand-alone measures that are designed to assess aspects of executive functioning (e.g., working memory, inhibition, planning, organization, cognitive flexibility, etc.). The D-KEFS' norming procedure used a standardized sample of 1,750 children, adolescents, and adult participants representative of 2000 U.S. Census data for age, sex, race and ethnicity, educational level, and geographic region, then stratified by these demographic factors and geographic region.

The Letter Fluency subtest of the DKEFS asks that participants say as many words as they can that begin with three specific letters (F, A, and S), under time-limited (1-minute duration) conditions. The Letter Fluency subtest aims to evaluate the effectiveness of patients' novel mental searching strategies, as well as imposing an effective mental structure on an unstructured task (Delis, Kaplan, & Kramer, 2001). The reliability of the DKEFS Letter Fluency

subtest for healthy children ranges between .68 and .81, depending on age group (Delis et al., 2001).

Assessment of fatigue. At the time of the evaluation, parents completed the PedsQL Multidimensional Fatigue Scale (PedsQL MFS), an 18-item questionnaire designed to assess fatigue in pediatric patients ages 2 to 18 years. The PedsQL MFS is offered in several age ranges, including 2-4, 5-7, 8-12, and 13-18 years. The PedsQL MFS is comprised of a 6-item General Fatigue Scale, a 6-item Sleep/Rest Fatigue Scale, and a 6-item Cognitive Fatigue Scale. For a sample of healthy children, internal consistency reliability for the PedsQL Multidimensional Fatigue Scale Total Score (parent-proxy-report: $\alpha = .95$), General Fatigue Scale (parent-proxy-report: $\alpha = .92$ parent), Sleep/Rest Fatigue Scale (parent-proxy-report: $\alpha = .90$), and Cognitive Fatigue Scale (parent-proxy-report: $\alpha = .96$) were adequate for both group and individual comparisons (Varni et al., 2004). Multidimensional fatigue symptoms will be assessed using the PedsQL MFS General, Sleep/Rest, and Cognitive Fatigue scales obtained through parent report.

Assessment of depression. Parents completed the Behavior Assessment System for Children, Second Edition (BASC-2) to assess depression symptoms in participants. The BASC-2 is a proxy-report measure which employs a comprehensive set of behavioral-rating scales designed to evaluate behavioral, social, emotional, and adaptive functioning in children and adolescents. The BASC-2 is offered in several forms, including the BASC-2 Child (6-11 years) and the BASC-2 Adolescent (12-18 years) Parent Rating Forms. The BASC-2 form was given to parents of participants based on age of the participant. Results of the BASC-2 are interpreted via multiple dimensional scales (Hyperactivity, Aggression, Conduct Problems, Anxiety Depression Somatization, Atypicality, Withdrawal, Attention Problems, Adaptability, Social Skills,

Leadership, etc.), as well as several composite scales (Externalizing Problems, Internalizing Problems, Behavioral Symptoms Index, Adaptive Skills, Activities of Daily Living, Functional Communication). BASC-2 reliability estimates for parent-ratings of children who belong to clinical populations (e.g., children with developmental, medical, and/or psychiatric conditions) and the general population are grouped together and range from .77 to .90 (Reynolds & Kamphaus, 2004). For the purposes of the proposed study, parent report of depression symptoms will be obtained using the BASC-2 Depression scale.

Assessment of physical functioning. The Pediatric Quality of Life Inventory (PedsQL) Generic Core is a 23-item, multidimensional scale designed to measure health-related quality of life (HRQOL) in pediatric patients ages 2 to 18 years. This instrument has 3 child self-report formats for ages 5-7, 8-12, and 13-18 and for parent-proxy report formats for ages 2-4, 5-7, 8-12, and 13-18. We will use the parent-proxy report in this study. For a sample of healthy children, internal consistency reliability for the PedsQL Physical Functioning scale (α = .89 for parent-proxy-report) was found to be acceptable (Varni et al., 2001). Physical functioning will be assessed using parent report of the Physical Functioning scale.

APPENDIX B
Tables

Table 1. *Demographic and Clinical Characteristics of MS and TM Groups*

	MS Group (n = 67)	TM Group (n = 53)	p-value (2-Tailed)
Age (Years)			
Mean (*SD*)	15.3 (2.5)	12.13 (3.4)	< .001*
Range	7–18	6–18	
Sex (*N*, % Female)	45 (67%)	30 (57%)	.24
Right-Handedness	61 (91%)	45 (85%)	.30
Time Since Onset (Months)			
Mean (*SD*)	13.63 (17.41)	28.77 (41.18)	.02*
Range	1–117	0–168	
Age at Onset (Years)			
Mean (*SD*)	14.24 (2.79)	9.62 (4.95)	< .001*
Range	4–18	0–17	
Physical Functioning			.009*
Mean (*SD)*	79.82 (25)	67.43 (23.77)	
Range	35–110	18–110	
Race (*N*, %)			.12
White	42 (63%)	42 (79%)	
Black or African American	14 (21%)	4 (8%)	
Asian	2 (3%)	1 (2%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (2%)	
Other	9 (13%)	5 (9%)	
Ethnicity (*N*, %)			.41
Hispanic or Latino	22 (33%)	13 (25%)	
Non-Hispanic or Latino	42 (63%)	35 (66%)	
Other	3 (4%)	5 (9%)	

Caregiver Primary Language	64 (96%)	49 (93%)	.70
English			

*Note: * = $p < .05$; Differences in age, time since onset, and age at onset assessed using independent samples t-tests; Differences in sex and handedness assessed using chi-square test; Differences in race, ethnicity, and caregiver primary language were assessed using Fisher's Exact test.*

Table 2. *Independent Samples T-Tests Between MS and TM Fatigue and Depression Scores*

	MS Group (*M*, SD)	TM Group (*M*, SD)	*T*-Test	*p*-value (2-Tailed)	Cohen's *d*
General Fatigue	69.45 (26.57)	70.53 (27.75)	-.208	.84	.38
Sleep/Rest Fatigue	74.03 (25.6)	82.65 (22.09)	-1.87	.06	.36
Cognitive Fatigue	74.81 (25.66)	84.43 (25.39)	-1.97	.05	.40
Depression	52.87 (16.53)	51.29 (11.23)	.59	.56	.11

*Note: Fatigue measured by PedsQL MFS (*M *= 100; SD = 15); Depression measured by BASC-2 Depression subscale (*M *= 50; SD = 10).*

Table 3. *Chi-Square Tests Between MS and TM Fatigue and Depression Scores*

	n	Chi-Square Value (*df* = 2)	*p*-value (2-Sided)
General Fatigue	111	.267	.29
Sleep/Rest Fatigue	111	2.75	.25
Cognitive Fatigue	111	5.12	.08
Depression	115	.30	.90

*Note: Fatigue measured by PedsQL MFS (*M *= 100; SD = 15); Depression measured by BASC-2 Depression subscale (*M *= 50; SD = 10). Differences in Depression were assessed using Fisher's Exact test.*

Table 4. *Proportions of Elevated Fatigue and Depression for MS and TM Groups*

	MS Group		TM Group	
	n	%	*n*	%
General Fatigue	62		49	
Mild	6	10%	10	20%
Severe	35	56%	23	47%
Total Elevated	41	66%	33	67%
Sleep/Rest Fatigue	62		49	
Mild	10	16%	8	16%
Severe	28	45%	16	33%
Total Elevated	38	61%	24	49%
Cognitive Fatigue	62		49	
Mild	12	19%	14	29%
Severe	28	45%	12	24%
Total Elevated	40	64%	26	53%
Depression	63		52	
At-Risk	10	16%	10	19%
Clinically Significant	6	10%	4	8%
Total Elevated	16	25%	14	27%

Note: Fatigue Total = Mild (1-2 SDs below the mean) and Severe Fatigue (2 or more SDs below the mean) proportions combined; Depression Total = At-Risk (1-2 SDs above the mean) and Clinically Significant (2 or more SDs above the mean) Depression proportions combined.

Table 5. *Measures Used in Cognitive Impairment Model*

Measure	Description	Scale
CVLT-C/II		
Trial 1-5 Total	Total verbal learning and recall across five trials	T-Score
Trial 1	Verbal learning and recall on first trial	Standard Score
Trial 5	Verbal learning and recall on fifth trial	Standard Score
Long-Delay Trial	Verbal learning and recall following 20-minute delay	Standard Score
Grooved Pegboard		
Dominant Hand	Fine-motor speed and dexterity using dominant hand	Standard Score
Non-Dominant Hand	Fine-motor speed and dexterity using non-dominant hand	Standard Score
Beery VMI	Copy geometric forms of increasing complexity	Standard Score
Beery VP	Accurately match geometric forms	Standard Score
Trail Making Test		
Part A	Connect letters in order by drawing lines quickly and accurately	Standard Score
Part B	Alternating connecting letters and numbers in order quickly and accurately	Standard Score
WISC-V/WAIS-III		
Symbol Search	Motor-based processing speed and visual discrimination	Scaled Score
Digit Span	Auditory attention and working memory for number recall	Scaled Score
SDMT Oral Version	Motor-free processing speed and visual discrimination	Standard Score
D-KEFS Letter Fluency Test	Rapid generation of words based on phonemic cue	Scaled Score

Note: T-Scores have mean of 50, SD of 10; Standard Scores have mean of 100, SD of 15; Scaled Scores have mean of 10, SD of 3.

Table 6. *Logistic Regression for Prediction of Cognitive Impairment*

Variable	B	SE	Wald	*p*-value	Odds Ratio	95% CI
General Fatigue	-.025	0.14	3.142	.08	.975	.95-1.03
Sleep/Rest Fatigue	.005	.011	.212	.65	1.005	.984-1.03
Cognitive Fatigue	.006	.010	.298	.56	1.006	.985-1.03
Depression	-.006	.010	.457	.50	.994	.975-1.01
Diagnosis	.991	.602	2.706	.10	2.693	.83-8.77
Age at Onset	.103	.091	.012	.91	1.001	.928-1.33
Time Since Onset	.001	.012	.012	.91	1.001	.978-1.03
Physical Functioning	-.017	.013	1.699	.19	.983	.959-1.01

*Note: CI = Confidence interval; Fatigue measured by PedsQL MFS (*M *= 100; SD = 15); Depression measured by BASC-2 Depression subscale (*M *= 50; SD = 10); Physical Functioning measured by PedsQL Generic Core Physical Functioning subscale (*M *= 100; SD = 15).*

Table 7. *Stepwise Logistic Regression for Prediction of Cognitive Impairment*

Variable	B	SE	Wald	*p*-value	Odds Ratio	95% CI
Depression	.033	.015	4.96	.03	1.03	1.004-1.064

*Note: CI = Confidence interval; Depression measured by BASC-2 Depression subscale (*M *= 50; SD = 10).*

Table 8. *One Sample T-Tests Comparing MS Group Means with Normative Means*

	M	SD	Mean Difference	*T*-Test	*p*-value (2-Tailed)	Cohen's *d*
General Fatigue	69.45	26.57	-30.55	-9.05	< .001*	1.15
Sleep/Rest Fatigue	74.03	25.60	-25.97	-7.99	< .001*	1.01
Cognitive Fatigue	74.81	25.66	-25.19	-7.73	< .001*	.98
Depression	52.87	16.53	2.87	1.38	.17	.17

*Note: * = p < .05; Fatigue measured by PedsQL MFS (*M *= 100); Depression measured by BASC-2 Depression subscale (*M *= 50).*

Table 9. *One Sample T-Tests Comparing TM Group Means with Normative Means*

	M	SD	Mean Difference	*T*-Test	*p*-value (2-Tailed)	Cohen's *d*
General Fatigue	70.53	27.75	-29.47	-7.43	< .001*	1.06
Sleep/Rest Fatigue	82.65	22.09	-17.35	-5.50	< .001*	.79
Cognitive Fatigue	84.43	25.39	-15.57	-4.29	< .001*	.61
Depression	51.29	11.23	1.29	.83	.41	.11

*Note: * = p < .05; Fatigue measured by PedsQL MFS (*M *= 100); Depression measured by BASC-2 Depression subscale (*M *= 50).*

Table 10. *Chi-Square Test of Proportions of Cognitive Status Classifications Between MS and TM*

	MS Group (n = 67)		TM Group (n = 53)		
	n	%	*n*	%	*p*-value (2-Tailed)
Non-Impaired	39	58%	42	79%	
Impaired	28	42%	11	21%	
					.02*

*Note: * = $p < .05$; Cognitive impairment defined using Huizenga et al., (2007) T^2 multivariate model.*

Table 11. *Chi-Square Test of Proportions of Fatigue and Depression by Cognitive Status*

	Non-Impaired		Impaired		
	n	%	*n*	%	*p*-value (2-Tailed)
General					.03*
Normal	30	41%	7	18%	
Mild	11	15%	5	13%	
Severe	32	44%	26	68%	
Sleep/Rest					.03*
Normal	39	53%	11	29%	
Mild	12	16%	6	16%	
Severe	22	30%	21	55%	
Cognitive					.09
Normal	33	45%	12	32%	
Mild	19	26%	7	18%	
Severe	21	29%	19	50%	
Depression					.12
Normal	61	77%	24	68%	
At-Risk	14	18%	6	16%	
Severe	4	5%	6	16%	

*Note: * = $p < .05$; Fatigue measured by PedsQL MFS; (Normal = less than 1 SD below the mean; Mild = 1-2 SDs below the mean; and Severe Fatigue = 2 or more SDs below the mean); Depression measured by BASC-2 Depression subscale (Normal = less than 1 SD above the mean; At-Risk = 1-2 SDs above the mean; and Clinically Significant = 2 or more SDs above the mean). Differences in Depression assessed using Fisher's Exact test.*

Table 11. *Measures Used in Cognitive Impairment Model*

Measure	Description	Scale
CVLT-C/II		
Trial 1-5 Total	Total verbal learning and recall across five trials	T-Score
Trial 1	Verbal learning and recall on first trial	Standard Score
Trial 5	Verbal learning and recall on fifth trial	Standard Score
Long-Delay Trial	Verbal learning and recall following 20-minute delay	Standard Score
Grooved Pegboard		
Dominant Hand	Fine-motor speed and dexterity using dominant hand	Standard Score
Non-Dominant Hand	Fine-motor speed and dexterity using non-dominant hand	Standard Score
Beery VMI	Copy geometric forms of increasing complexity	Standard Score
Beery VP	Accurately match geometric forms	Standard Score
Trail Making Test		
Part A	Connect letters in order by drawing lines quickly and accurately	Standard Score
Part B	Alternating connecting letters and numbers in order quickly and accurately	Standard Score
WISC-V/WAIS-III		
Symbol Search	Motor-based processing speed and visual discrimination	Scaled Score
Digit Span	Auditory attention and working memory for number recall	Scaled Score
SDMT Oral Version	Motor-free processing speed and visual discrimination	Standard Score
D-KEFS Letter Fluency Test	Rapid generation of words based on phonemic cue	Scaled Score

Note: T-Scores have mean of 50, SD of 10; Standard Scores have mean of 100, SD of 15; Scaled Scores have mean of 10, SD of 3.

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